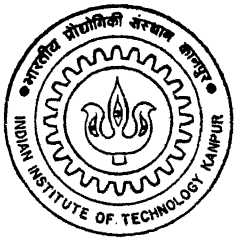
MEVINIC ACID ANALOGS : DESIGN, SYNTHESIS AND ENZYME CATALYSED OPTICAL RESOLUTION

by

KAMAL KISHORE KAPOOR



DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY KANPUR

JULY, 1995

MEVINIC ACID ANALOGS: DESIGN, SYNTHESIS AND ENZYME CATALYSED OPTICAL RESOLUTION

A Thesis Submitted
in Partial Fulfilment of the Requirements
for the Degree of
DOCTOR OF PHILOSOPHY

by

KAMAL KISHORE KAPOOR

to the

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY KANPUR

JULY, 1995

DEDICATED

TO

Maanji and Bauji

STATEMENT

I hereby declare that the matter embodied in this thesis entitl ed,**"MEVINIC ACID ANALOGS : DESIGN, SYNTHESIS AND ENZYME CATALYSED OPTICAL RESOLUTION"** is the result of investigation carried out by me in the Department of Chemistry at Indian Institute of Technology (I.I.T.) Kanpur, India, under the supervision of **Dr. Veejendra K. Yadav.**

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the finding of other investigators.

KAMAL KISHORE KAPOOR

I.I.T. KANPUR

JULY, 1995.

CERTIFICATE I

It is certified that the work contained in this thesis entitled, "**MEVINIC ACID ANALOGS : DESIGN, SYNTHESIS AND ENZYME CATALYSED OPTICAL RESOLUTION**" has been carried out by Mr. Kamal Kishore Kapoor, under my supervision and the same has not been submitted elsewhere for a degree.

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July, 1995

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CERTIFICATE II

This is to certify that Mr. Kamal Kishore Kapoor has satisfactorily completed all the courses required for the Ph.D. Programme at our department. These courses include:

CHM 602 ADVANCED ORGANIC CHEMISTRY

CHM 605 PRINCIPLES OF ORGANIC CHEMISTRY

CHM 611 PHYSICAL ORGANIC CHEMISTRY

CHM 624 MODERN PHYSICAL METHODS IN CHEMISTRY

CHM 625 PRINCIPLES OF PHYSICAL CHEMISTRY

CHM 645 PRINCIPLES OF INORGANIC CHEMISTRY

CHM 800 SPECIAL SEMINAR

CHM 801 GENERAL SEMINAR

CHM 900 PH.D. THESIS

Mr. Kamal Kishore Kapoor has successfully completed the written and oral qualifying examinations in January, 1992. He delivered his "STATE OF ART" seminar in April, 1992.

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July, 1995.

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The caring and affectionate attitude of other friends Debnath and Arpita, Damu and Uma, Subrato and Indranidi, Sangeeta, Sunil Panjabi, Sundar, Prabhucharan, Sonu and Jai, Nachiketa, Govind, Madhav, Sanchita, Zahida, Beena, Ravikant, Ajit, Simant, Baldevji, Balvinder, Jayateerth, Venkatraman, Chavli, Shafi, Punnyamurthy, Kumareshwaran, Raju, Neeraj, Ramesh (Talevali) and whose names I have not mentioned cannot be devoid of my indebtedness to them.

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Kushwah Saheb and Shukla Saheb have been moral support and guardian-like to me. I am grateful to them for the timely help they have rendered at various occasions. Thanks are due to Josans and Sardarji's for their affectionate treatment during dull moments.

I intently feel grateful to the sustaining force in the words of Jijaji-Didiji, Indu, Priya and Raju. But for that my research career would have had another history.

-Kamal Kishore Kapoor

The thesis entitled,"MEVINIC ACID ANALOGS: DESIGN, SYNTHESIS AND ENZYME CATALYSED OPTICAL RESOLUTION" is divided into five chapters. The title of each chapter and the related summary is given below.

CHAPTER 1 : Introduction

This chapter gives a brief account of various synthetic approaches known in the literature for the construction of the β-hydroxy-δ-lactone portion of mevinic acids.

CHAPTER 2 : 5-Oxo-2-phenyl-1,3-dioxan and its derivatives as precursors for the synthesis of mevinic acid analogs

In this chapter we describe few synthetic approaches attempted for the preparation of either 5-Oxo-2-phenyl-1,3-dioxan or its derivatives as precursors to mevinic acid analogs. These include the oxidation of

(a) 5-hydroxy-2-phenyl-1,3-dioxan using conventional oxidising agents,

(b) 2-phenyl-5-tosyloxy-1,3-dioxan using Kornblum reaction and

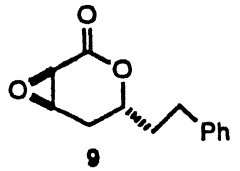
(c) 5-bromo-2-phenyl-4-(2-phenylethyl)-1,3-dioxan employing, again, the Kornblum reaction in the presence of a halophilic metal ion such as Ag^+.

CHAPTER 3 : Synthesis of mevinic acid analaogs

Here we delineate the synthesis of mevinic acid analogs via two new routes. Both the routes share 3,4-dehydro-6-(2-phenylethyl)-tetrahydropyran-2-one as a common intermediate:

(a) Diastereoselective epoxidation of 3,4-dehydro-6-(2-phenylethyl) tetrahydropyran-2-one

This route employs newly developed oxidation system **t-BuOOH/DBU** for diastereoselective epoxidatgion of the above intermediate to produce the corresponding α,β-epoxy-6-(2-phenylethyl)tetrahydropyran-2-one **9**. Regioselective cleavage of the oxirane ring in compound **9** produces a diastereomeric mixture of 4-hydroxy-6-(2-phenylethyl)tetrahydropyran-2-one **14**. This disastereomeric mixture was acetylated and resolved by pig liver acetone powder (PLAP).



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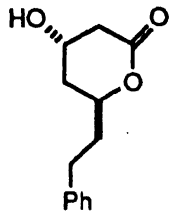

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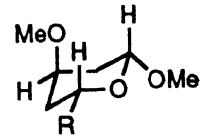
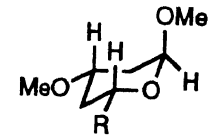


19a



19b

(b) Reaction of MeOH with 2-alkoxy substituted 3,4-dehydro-6-(2-phenylethyl)tetrahydropyran : Revelation of acyclic 1,3-diastereoselection

The second route utilises the 1,3-acyclic diastereoselection in the reaction of MeOH with 3,4-dehydro-2-hydroxy-6-(2-phenylethyl)-tetrahydropyran as a 84:16 mixture of *arabino* **19a** a*nd xylo* **19b** species. The related *ribo* and *lyxo* structures were absent. The preponderance of the *arabino* structure over *xylo* is of interest. In a related study on 6-carbomethoxy derivative by Zamojsby *et al.*, the *arabino/xylo*distribution was 1:1. Comprehensive transition state models taking into account the dipolar effects

and Felkin's earlier observations are discussed. The above bismethoxy tetrahydropyran mixture was further transformed into the 4-hydroxy derivative. In the major constituent, the relative stereochemistry at positions 4 and 6 is that present in mevinolins.

CHAPTER 4 : Newer oxidation reagents

(a) t-BuOOH and KF-impregnated Al_2O_3

(b) t-BuOOH and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU)

The failure of known methods for the epoxidation of 3,4-dehydro-6-(2-phenylethyl)tetrahydropyran-2-one functioned as prelude to the development of newer oxidation systems. The first oxidation system which we developed is **t-BuOOH** and **KF-impregnated Al_2O_3**. Whereas the reagent system failed to oxidise the α,β-unsaturated-δ-lactone, it worked very well with a variety of other electron deficient olefins. The failure of this system with enelactones was presumably due to the poor Michael acceptibility of such systems and also, probably, due to the complexed nature of t-butylperoxy anion with Al_2O_3. We looked at the complexed aspect first and envisioned to replace **KF/Al_2O_3** by **DBU**. This system not only succeeded in bringing epoxidation of above unsaturated δ-lactone in very good yield,the reaction was highly diastereoselective as well. This method also provides easy access to epoxides from a wide spectrum of electronically deficient alkenes. Numerous other interesting observations have been made and constitute part of this chapter.

CHAPTER 5 : Changing the pharmacrophore : DBU promoted isomerisation of unsaturated lactones and its application to the construction of structurally interesting species

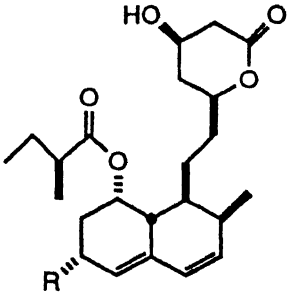
This chapter involves the exploration of DBU promoted isomerisation of 7-membered ring unsaturated lactones. ^{1}H NMR monitoring of the isomerisation reaction reveals that β,γ-unsaturated-7-membered lactones are slightly more stable than the conjugated counterparts. The deconjugated 7-benzyl substituted 7-membered ring lactone was further used in the construction of interesting molecules having close resemblance with part structures in certain natural products. Attempts to obtain a relative of mevinic acid analog by bringing the changes in pharmacophore portion are also described.

CONTENTS

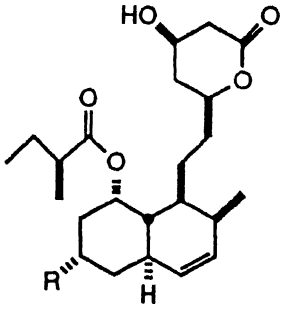
CHAPTER 1

INTRODUCTION

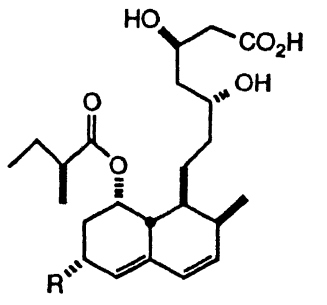
In 1976, Endo and coworkers[1] at the Sankyo Laboratories and Brown and coworkers[2] at Beecham Pharmaceuticals isolated a potent competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase) from the metabolites of *Penicillium citrinum* and *P. brevicompactum*, respectively. The new compound **1** was named ML 236B by the Japanese group and compactin by British workers. A second, more active compound, mevinolin **2**, was isolated from *Monascus ruber* by Endo[3] and from *Asperigillius terreus* by Alberts and coworkers[4] at Merck, Sharpe and Dohme. Two other related compounds, dihydrocompactin **3**[5] and dihydromevinolin **4**[6], were subsequently isolated as minor metabolites from the



1: R = H
2: R = Me



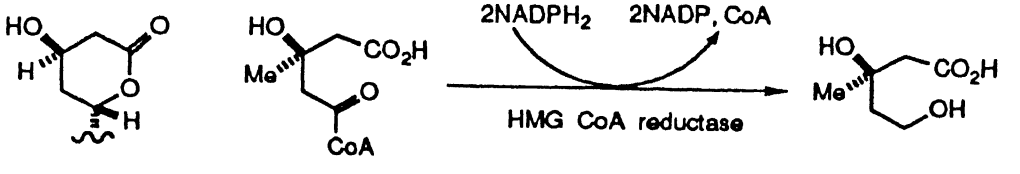
3: R = H
4: R = Me



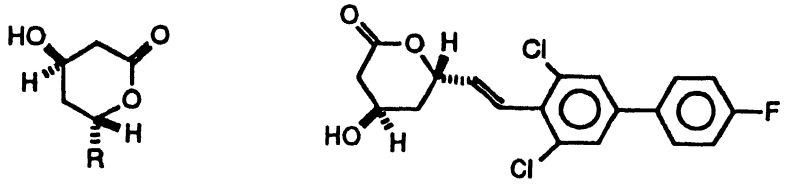
5: R = H
6: R = Me

cultures of these fungi. These fungal metabolites, distinguished by a highly functionalised decalin unit and β-hydroxy-δ-lactone portion linked by an ethylene bridge, are members of a family of compounds called the 'mevinic acids'. The Merck group also discovered that the active forms of compactin and mevinolin are the respective open chain dihydroxy acids **5** and **6**.

Since discovery, both compactin and mevinolin have attracted considerable global attention due to their biological activity as inhibitors of HMG CoA reductase. HMG CoA reductase is a major rate limiting enzyme responsible for the reduction of HMG CoA to mevalonic acid.[7,8] This acid is a crucial intermediate in the biosynthesis of cholesterol. Mevinolin, presently marketed under the trade name Mevacor by the Merck group, is one of the most clinically useful hypocholesterolemic agents. It is manufactured by a fermentation process. Dihydromevinolin, which exhibits biological activity similar to mevinolin, is produced in small quantities during the fermentation; it has, therefore, not been developed as a clinical candidate. The lactone function **7** of the mevinic acids is essential for inhibition because it, in its open form, closely mimics mevalonic acid. The role of the decalin unit is purely that of hydrophobic in nature[9].



7 HMG CoA Mevalonic acid



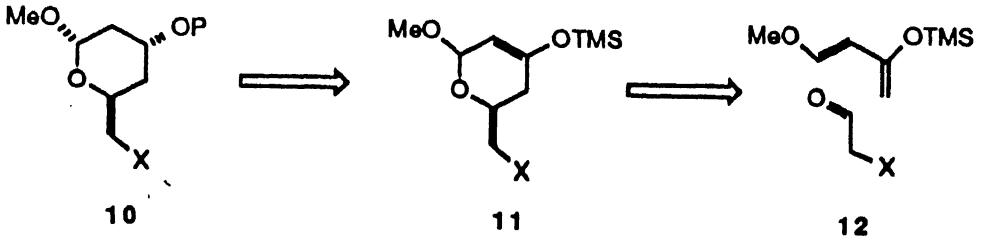
8 **9**

The design of the synthetic analogs of mevinic acids[10] has been governed by two major considerations, namely, the requirement for a lactone function **7** and the desirability of having a much

simpler array in place of the complex decalin systems present in the natural products. The related analogs **8** of mevinic acids were generally most active when the substitutent R was arylethyl or (E)-arylethenyl[11]; an example being the material **9** which, in its dihydroxy acid form, displays 2.8 times the activity of natural compactin **1** in HMG CoA reductase inhibition[12]. *For these reasons, interest among the chemists is generated towards the stereocontrolled synthesis of lactone* **8** *with different R substituents.* We present here a focussed account of the work on mevinic acid analogs. The literature covered is up until 1994.

Danishefsky and coworkers[13a] described the synthesis of the masked pyranone segment of compactin using Lewis acid catalysed cyclocondensation of a silyloxy diene with an aldehyde as the key synthetic maneuvre. The synthetic strategy is shown in Scheme 1. Silyl enol ether **11**, the product of formal cycloaddition of heterodienophile **12** and Danishefsky's diene, is envisioned as a precursor to **10**.

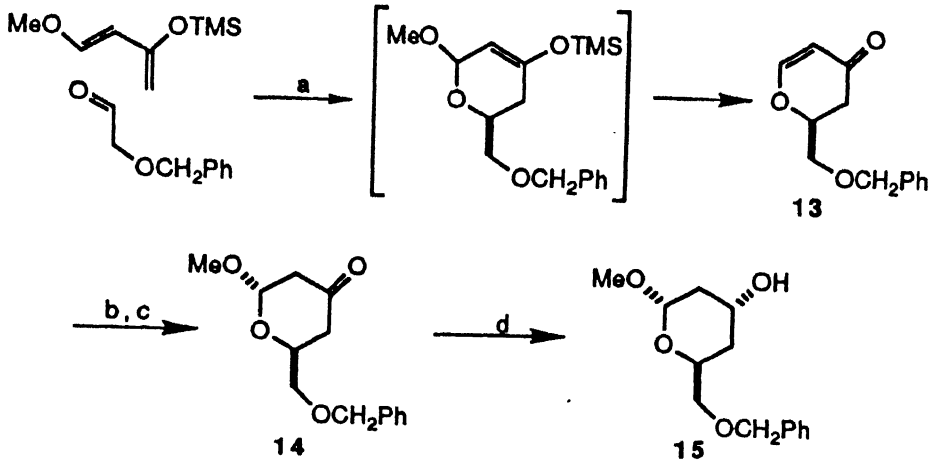
Scheme 1



10 **11** **12**

To this end, reaction of benzyloxyacetaldehyde with 1-methoxy-3-trimethylsilyloxybutadiene in the presence of anhydrous $ZnCl_2$ proceeds to give the adduct **13** (Scheme 2).

Scheme 2



(a) $ZnCl_2$, PhH, rt; 87% (b) MeOH, HCl; 69% (c) Acetone, HCl
(d) L-Selectride; 88%

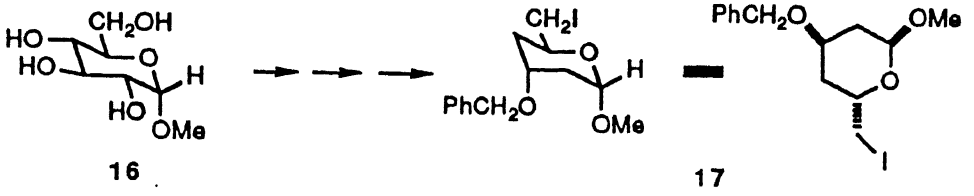
Treatment of **13** with methanolic HCl produces a methylglycoside with concomitant ketalization; deketalization with acetone containing a trace of HCl affords **14**. Reduction of **14** with **L**-selectride proceeds with selective equatorial delivery of hydride ion to give the desired racemic synthon **15**. By starting with an optically active acetonide of glyceraldehyde rather than with benzyloxyacetaldehyde, the synthesis may be manipulated so as to provide an optically active and protected version of **15**[13b].

Some chemists have been struck by the structural relationship between "compactin lactone" and glucose. Thus, Prugh and Deana[14] converted methyl-α-D-glucopyranoside **16** into enantiomerically pure iodide **17** in a reaction sequence entailing 12 steps (Scheme 3). Benzylation of the benzylidene **18**, readily obtained from α-D-glucopyranoside **16**, provides **19** (Scheme 4). Hydrolysis of the benzylidene group gives a diol which is selelectively protected to

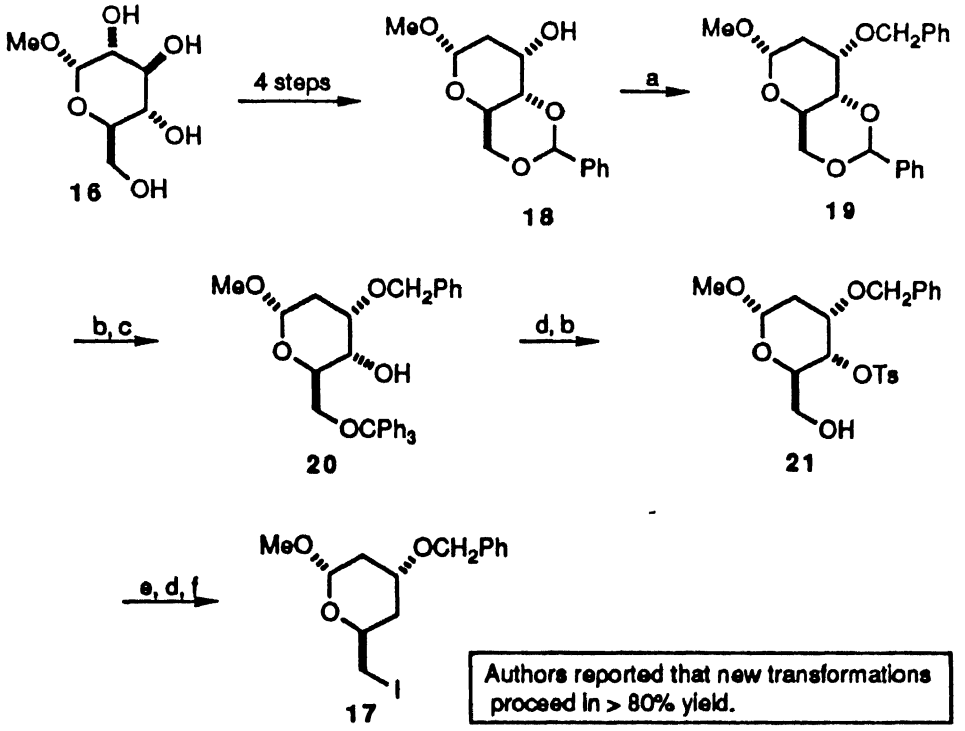
give hydroxy trityl ether **20**. Tosylation and hydrolysis of trityl ether gives **21**. This is reduced with sodium borohydride in DMSO to obtain a 2,4-dideoxy derivative which, on sequential tosylation and iodide displacement, affords the desired synthon **17**.

The triacetyl glucal **22** is much more expensive than the methyl glucoside **16**. A key intermediate, Corey epoxide **23**, is first prepared from **22**[15] and then converted in the sequence shown in Scheme 5 into a 9:1 mixture of anomers **24** and **25**. Chromatographic removal of the minor product **25**, tosylation of **24**, and subsequent application of the Finkelstein reaction affords iodide **26**[16].

Scheme 3



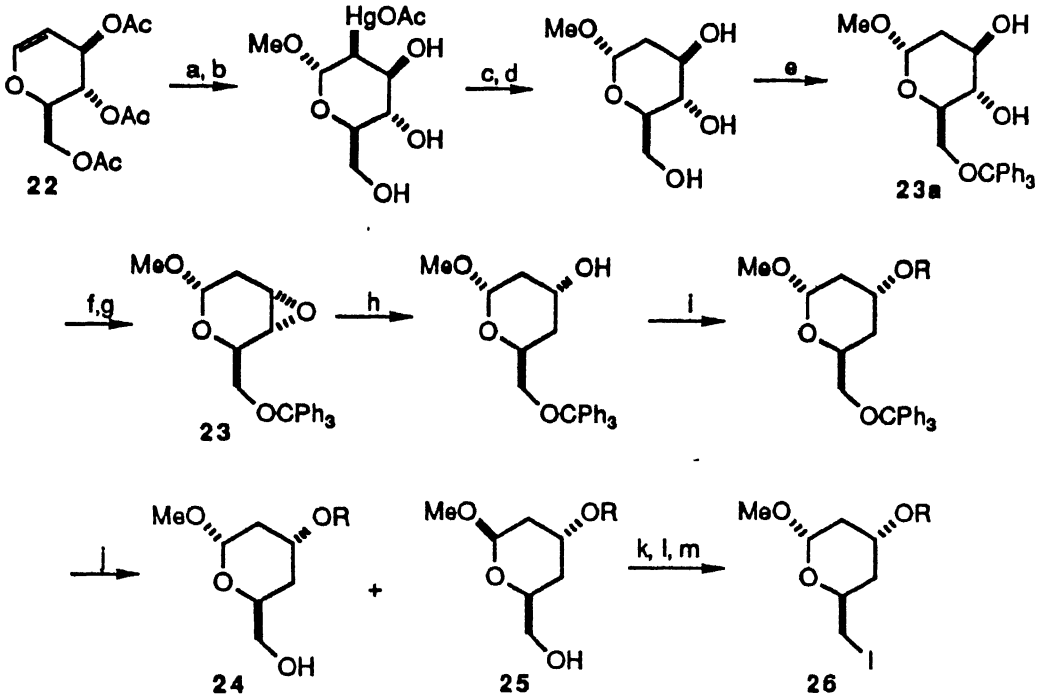
Scheme 4



(a) NaH, $PhCH_2Cl$, DMF (b) 70% TFA (aq), CH_2Cl_2 (c) Ph_3CCl, Pyridine
(d) TsCl, Pyridine (e) $NaBH_4$, DMSO (f) NaI, acetone

Clive and coworkers[17] utilized L-malic acid derivative **27** as a precursor to lactone synthon **32** (Scheme 6). Benzylation of **27** and hydrolysis of the acetonide afford monoprotected triol **28**.

Scheme 5

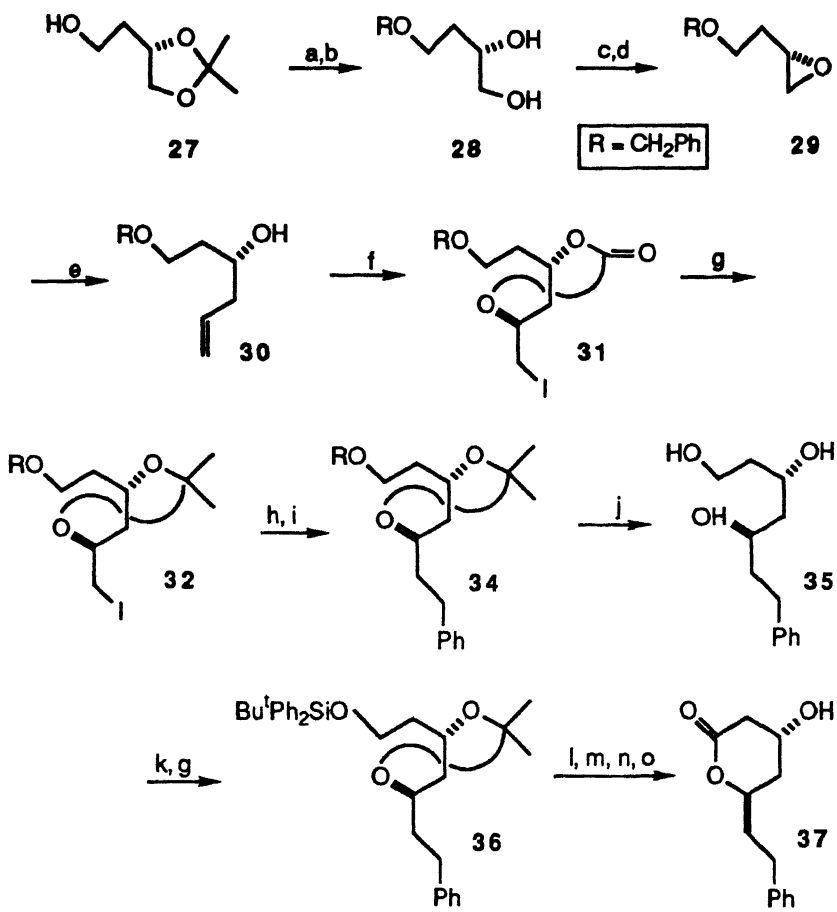


Ar = 2,4,6-triisopropylphenyl
R = $SiPh_2Bu^t$
Im = N- Imidazole

(a) NaOMe, MeOH (b) $Hg(OAc)_2$, MeOH (c) NaCl (d) $NaBH_4$ (e) Ph_3CCl (f) $ArSO_2Im$
(g) NaH ; 62% from **22** (h) $LiAlH_4$; 95% (i) NaH , Bu^tPh_2SiCl ; 92% (j) TsOH ; 89%
(k) chromatographic separation (l) TsCl , Pyridine (m) NaI , acetone ; 90% for steps l & m.

Mesylation and subsequent treatment with Triton B provides optically active epoxide **29** which is opened with vinylmagnesium bromide to obtain hydroxy olefin **30**. The lithium alkoxide of **30**

Scheme 6

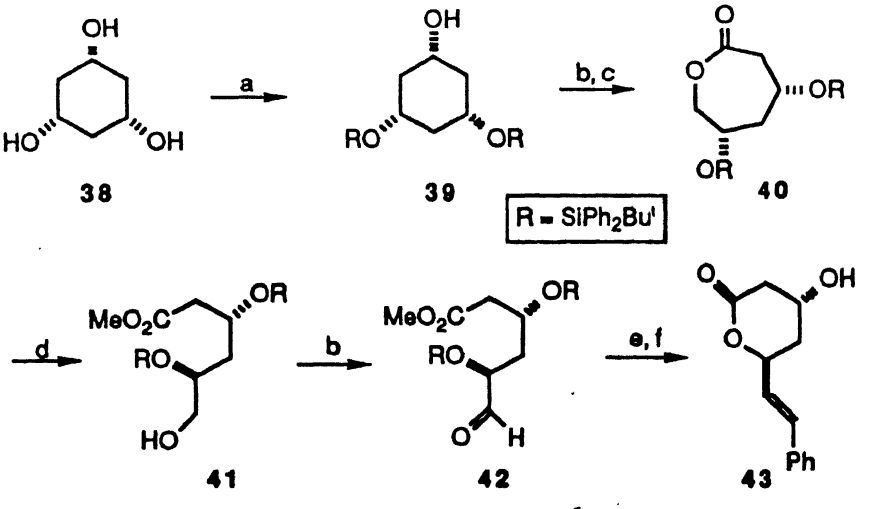


(a) NaH , DM F , $PhCH_2Br$ (b) AcOH-H_2O , 50 °C , 1h ; 86% for two steps (c) MsCl , pyridine (d) Triton B ; 65% for c & d (e) H_2C=CHMgBr ; 92% (f) n-BuLi , CO_2 , I_2 ; 69% (g) acetone , p-TSA (h) p-$MeC_6H_4SO_2CH_2Ph$ (33), KH , DM F, rt , 3h (i) 6% Na-Hg , MeOH ; 78% for steps h & i (j) Me_3SiI ; 73% (94% with one recycling of 34) (k) Bu^tPh_2SiCl (l) Bu_4NF (m) Collin's oxidn (n) PDC , DMF (o) HCl , CH_2Cl_2 ; 33% from 35.

is treated sequentially with CO_2 and I_2 to produce the 3(S),5(S)-iodo carbonate **31**. Hydrolysis of **31** with simultaneous acetonide formation followed by chromatographic purification gives pure acetal_ **32**. Coupling of **32** and sulfone **33** followed by desulfonylation affords the adduct **34**. This is deprotected to give the triol **35**. Oxidation of **35** with Fetizon's reagent (Ag_2CO_3/celite) affords **37** in poor yield (20%). Therefore, a multi-step procedure is employed. Selective protection of primary alcohol and acetonide formation produces **36**. Desilylation and subsequent oxidation and lactonization provide the desired lactone **37** in 33% overall yield from **35**.

Prasad and Repic[18] have synthesized the lactone system beginning with *cis*-cyclohexane-1,3,5-triol **38** (Scheme 7). Conversion to bis silyl ether **39** followed by PCC and Baeyer-Villiger oxidations, in that order, afford lactone **40** in

Scheme 7

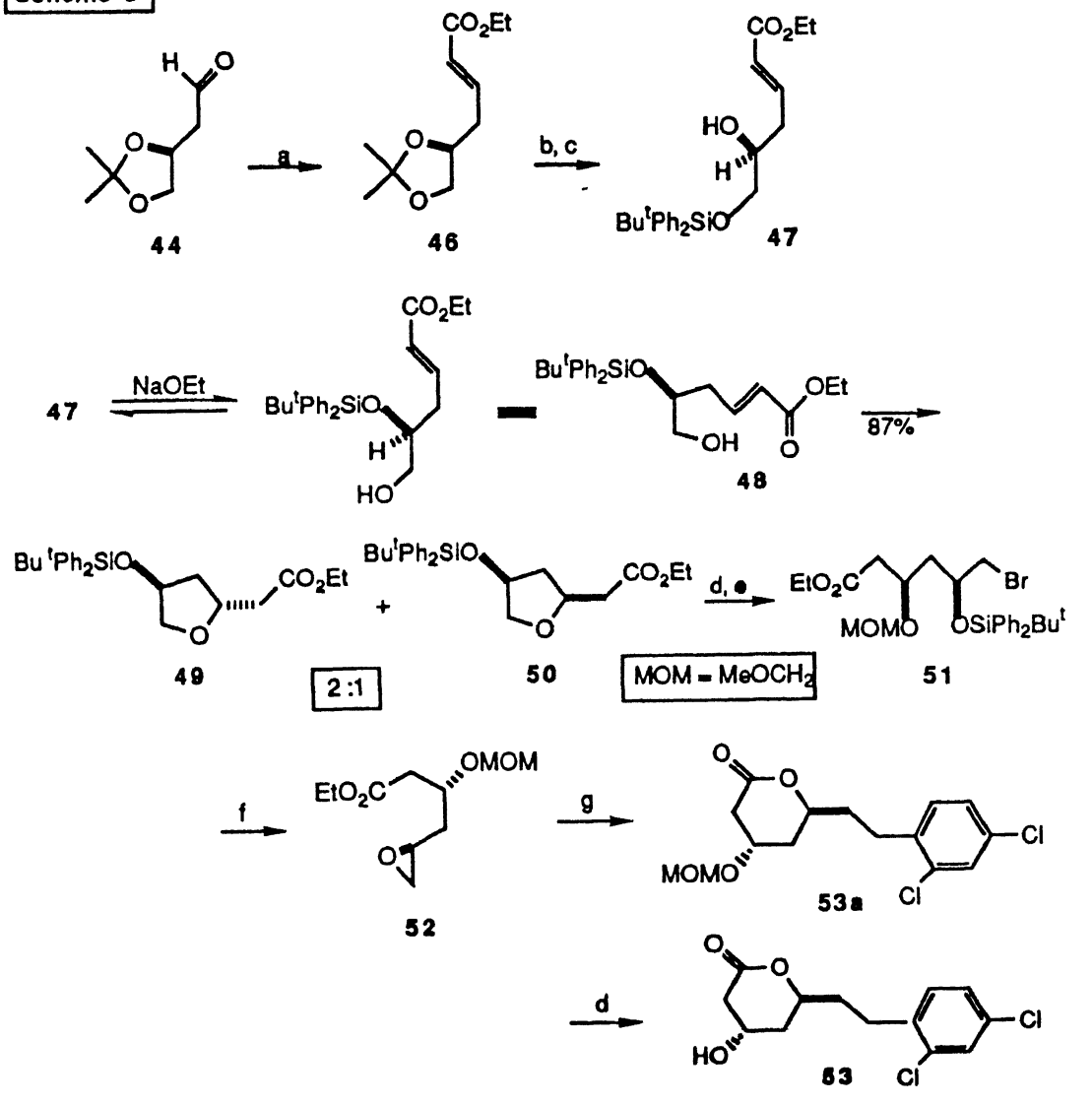


(a) $ClSiPh_2Bu^t$, Imidazole, DMF; 40% (b) PCC; 93%
(c) m-CPBA, $NaHCO_3$; 77% (d) MeOH, F_3CCO_2H; 95%
(e) $PhCH=PPh_3$, THF; 77% (f) n-BuNF, AcOH, THF; 45%

28% overall yield. Methanolysis and oxidation of the resulting hydroxy ester **41** provide aldehyde **42**. Wittig coupling and desilylation furnish the unmasked lactone **43**.

Guindon and coworkers[19] have published an approach for the synthesis of an optically active synthon for the lactone portion

Scheme 8

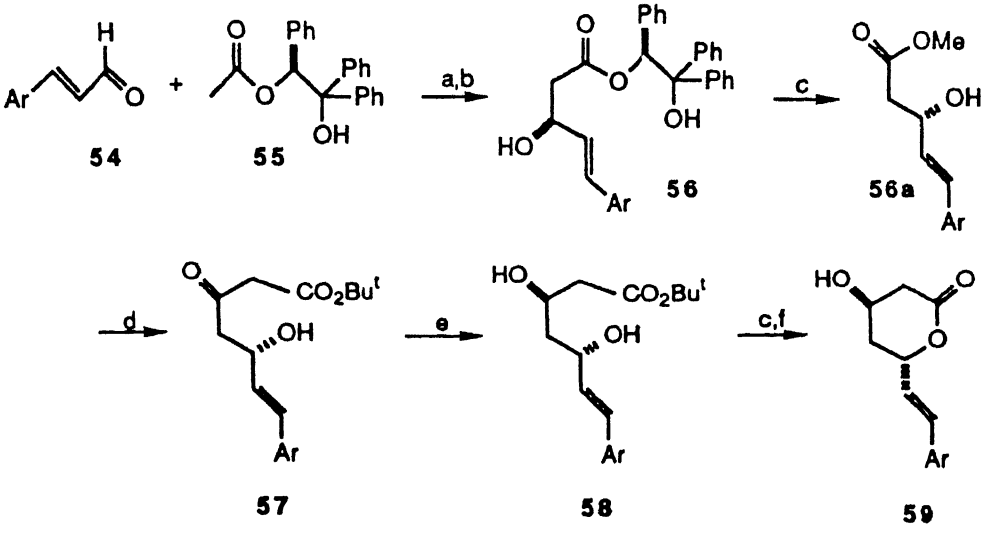


(a) Ph_3PCHCO_2Et (45) ; 84% (b) 1N HCl (aq) , THF (c) t-$BuPh_2SiCl$, Et_3N, DMAP, CH_2Cl_2 , rt
(d) Me_2BBr , CH_2Cl_2 ; 82% (e) MOMCl, I-Pr_2NEt, DMAP , CH_3CN ; 94% (f) n-Bu_4NF, THF ; 80%
(g) $R_2CuMgBr$, Et_2O , - 78 °C; then - 23 °C, 1h, quantitative

of mevinic acids utilizing L-malic acid aldehyde **44** (Scheme 8).

Condensation of **44** with stabilized phosphorane **45** provides unsaturated ester **46**. Hydrolysis of the acetonide moiety and selective silylation of primary alcohol affords mono-protected diol **47**. Treatment of **47** with catalytic ethoxide establishes an equilibrium with its isomer **48**. Ensuing intramolecular Michael reaction displaces the equilibrium, and tetrahydrofurans **49** and **50** are obtained in 2:1 ratio. Cleavage of **49** with dimethylboron bromide proceeds regiospecifically to produce, after protection, bromide **51**. Cleavage of the silyl ether affords directly the epoxide **52** which is opened regioselectively upon treatment with cuprates. Subsequent acid-catalysed cyclization and umnasking of the hydroxy group afford the hydroxy lactone **53**.

Scheme 9



54 **55** **56** **56a** **57** **58** **59**

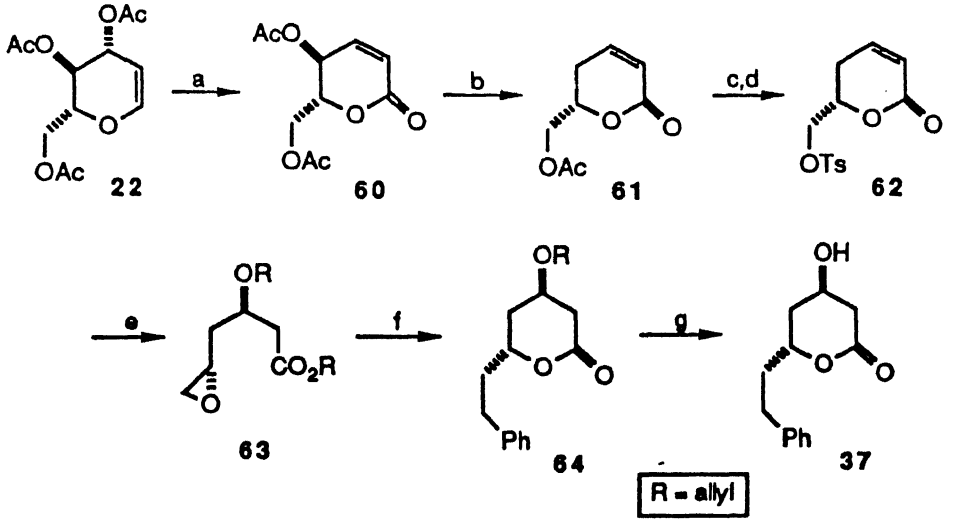
Ar = 2,4-bismethyl-6-(4-fluoro-3-methylphenyl)phenyl

(a) LDA, THF (b) $MgBr_2$; 93% (c) NaOMe, MeOH; 95% (d) lithio-t-butyl-acetate, THF, -30 °C - -40 °C; 90% (e) Et_3B, $NaBH_4$, THF-MeOH, -78 °C; 93% (f) acidification, pH 3.8; 85%.

Lynch and coworkers[20] have accomplished synthesis of the lactone **59** utilising the diastereoselective Aldol reaction followed by a Claisen condensation for the generation of the 5(S) stereocenter of keto-alcohol **57** from aldehyde **54** (Scheme 9). Condensation of aldehyde **54** with Mg(II) enolate of **55** following the procedure of Braun and Devant[21] produces the diastereoisomers **56** (SS:SR = 97:3), which upon sequential transesterification with NaOMe and treatment with lithio-t-butylacetate gives keto-alcohol **57**. The 5(S)-hydroxy function directed reduction of β-keto functionality in **57** affords the diol **58**. This, after saponification is acidified to give lactone **59** in 85% yield [3(R)5(S):3(S)5(R)= 97:3].

Roth and Roark[22] have utilised the stereoselective Michael addition[23] of alcohol to 6-tosyloxymethyl-5,6-dihydro-2H-pyran-2-

Scheme 10

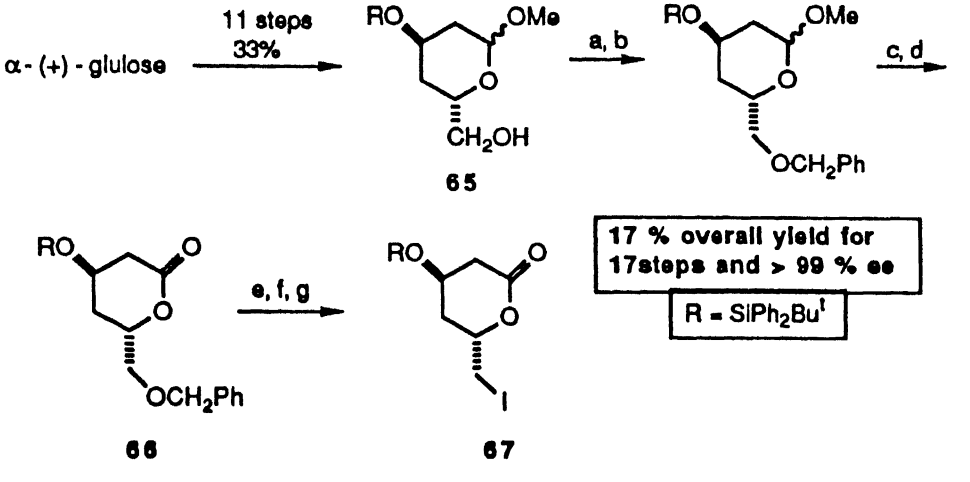


(a) PCC ; 85% (b) Zn-AcOH and then Et_3N ; 92% (c) 2N HCl (d) TsCl ; 92% for steps c & d (e) $H_2C = CHCH_2ONa$, allyl alchol ; 87% (f) $PhCH_2MgCl$, CuBr-Me_2S ; 73% (g) 10% Pd-C , dioxane : H_2O = 2:1 ; 50%

one **62** to afford the key chiral epoxide synthon **63** for the lactone portion of mevinic acids. To this end, once again commercially available glucal **22** on treatment with PCC affords the unsaturated lactone **60** (Scheme 10). Reductive deconjugation with Zn-AcOH followed by reconjugation with Et_3N produces 5-deoxygenated lactone **61**. Hydrolysis and tosylation gives the tosylate **62** which on reaction with sodium allyl alcoholate produces the key chiral epoxide **63**, a result of strereoselective Michael addition and epoxide formation. Reaction of epoxide **63** with dibenzyl cuprate followed by deprotection gives the lactone **37**.

Baader and coworkers[24] have reported the synthesis of lactone **67** utilising "chiral pool" approach (Scheme 11). The starting material **65** was obtained from α-D-(+)-glucose in 11 steps by known

Scheme 11



(a) n-BuLi, HMPT, -70 °C (b) $PhCH_2Br$, -70 to 25 °C; 95% (c) AcOH-H_2O-THF; 86% (d) CrO_3, pyridine, CH_2Cl_2; 94% (e) Pd-C, H_2; 92% (f) TsCl, pyridine; 80% (g) NaI, acetone; 91%.

methods[15,16a]. Protection of OH in **65**, hydrolysis of the lactol ether and subsequent oxidation of the lactol gives **66**. Reductive debenzylation, subsequent tosylation and iodide displacement produces **67**.

Johnson and Senanayake[25] have employed the optically active appropriately functionalised polyhydroxylated seven-membered ring intermediate **72** for the synthesis of either (-) or (+)-compactin analogs. The strategic intermediate **72** is obtained in seven steps from tropone **68** in 49% overall yield as outlined in Scheme 12.

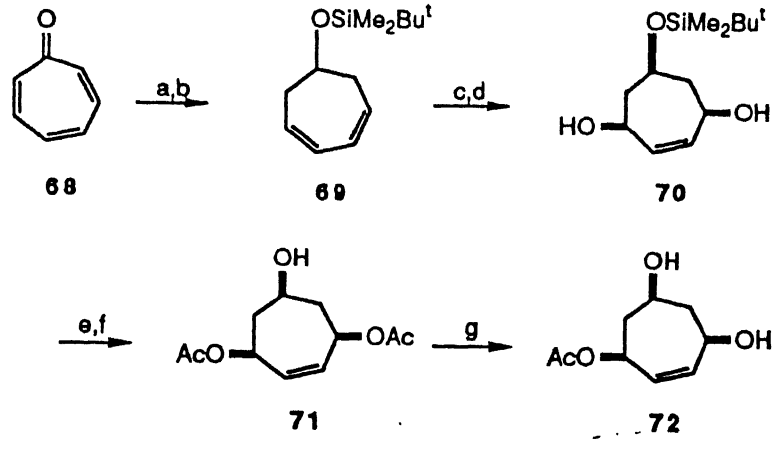
Tropone **68**, on reduction with $NaBH_4$, undergoes 1,8-hydride delivery to furnish a product which subsequently is converted into the t-butyldimethylsilyl ether **69**. Treatment of **69** with singlet oxygen gives a 5:1 (*syn/anti* mixture of *endo* peroxides. The major isomer, after chromatographic separation, is reduced to diol **70**. Meso acetate **71** is acquired by a two step sequence involving diol protection as the diacetate followed by silyl ether deprotection. Enzymatic hydrolysis of meso diacetate **71** gives **72** which is elaborated into compactin analogs (-)- and (+)-**37** (Scheme 13).

Key compound **72** is converted to enone **73** by protecting group manipulation followed by PDC oxidation. The assembly of the desired silyl enol ether **74** is accomplished by MeCu-catalysed hydroalumination with Dibal-H followed by trapping the aluminate with chlorotrimethyl silane[26]. Without purification, this labile substrate is ozonized and the crude product is treated with $NaBH_4$ followed by CH_2N_2 to give hydroxy ester **75**. Tosylation of **75** followed by sequential exposure to lithium diphenylcuprate and HF delivers (-)-**37**.

For preparation of lactone (+)-**37** (natural compactin analog), **72** is transformed into enone 76 via chemoselective oxidation followed by hydroxy protection as silyl ether. The enone **76** affords, on treatment with catalytic MeCu and Dibal-H followed by MeLi a bisaluminate species, which is reacted with t-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) to give **77**. Silyl enol **77** is transformed into natural compactin analogue (+)-**37** in a series of routine manipulation as described in Scheme 13.

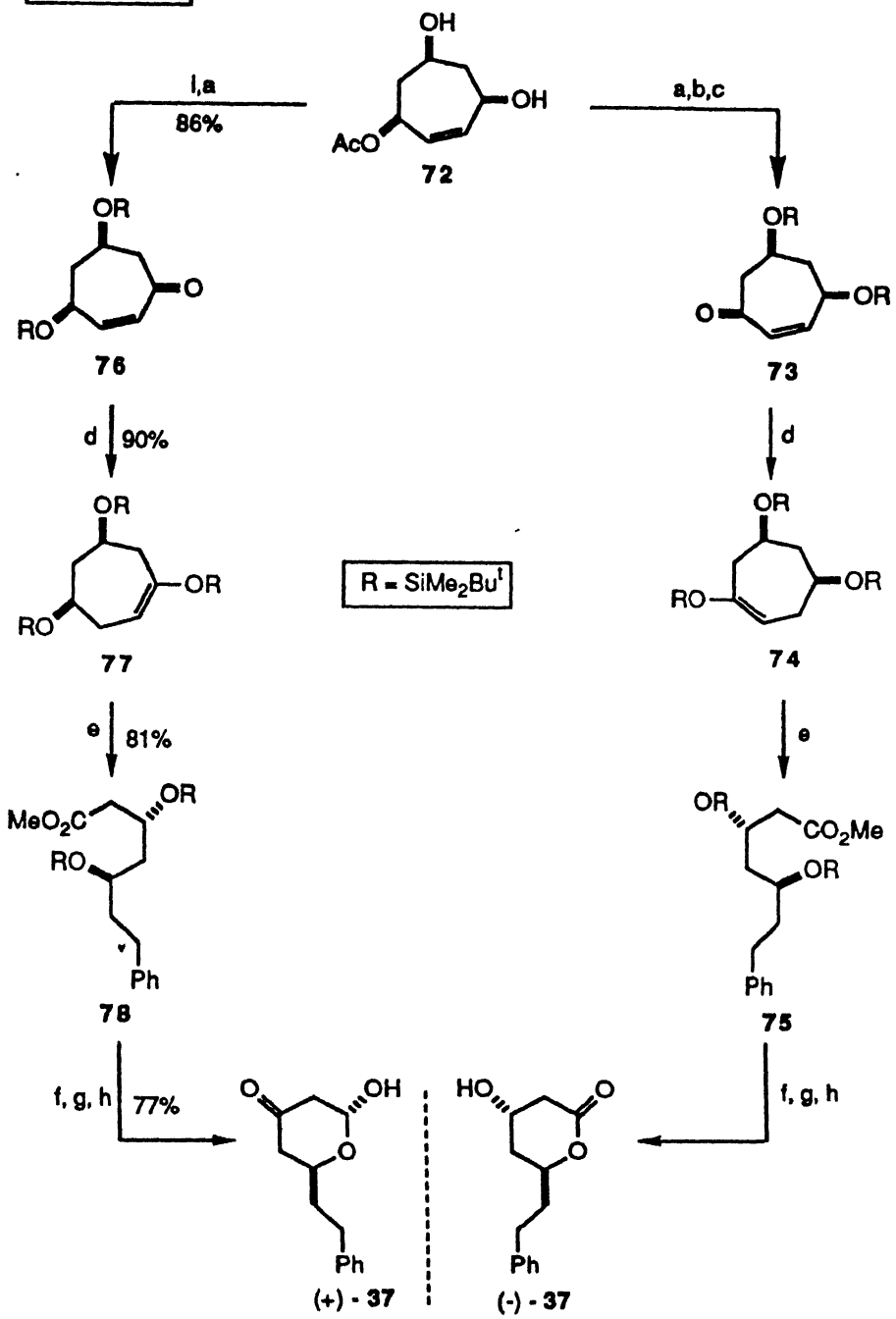
Takano and coworkers[27] have developed an approach for the facile chiral synthesis of lactone portion **87** from

Scheme 12



(a) $NaBH_4$, MeOH, H_2O (b) $Bu^t Me_2SiCl$, imidazole, DMF; 85% for steps a & b
(c) O_2, hv, *meso* tetraphenylporphine (d) Zn - AcOH or SmI_2, THF; 77% for steps c & d (e) Ac_2O, Et_3N, DMAP (f) HF, Pyridine, CH_3CN; 96% for steps e & f
(g) electric eel acetylcholinesterase aq phosphate pH 6.9 buffer, 25 °C; 79%.

Scheme 13

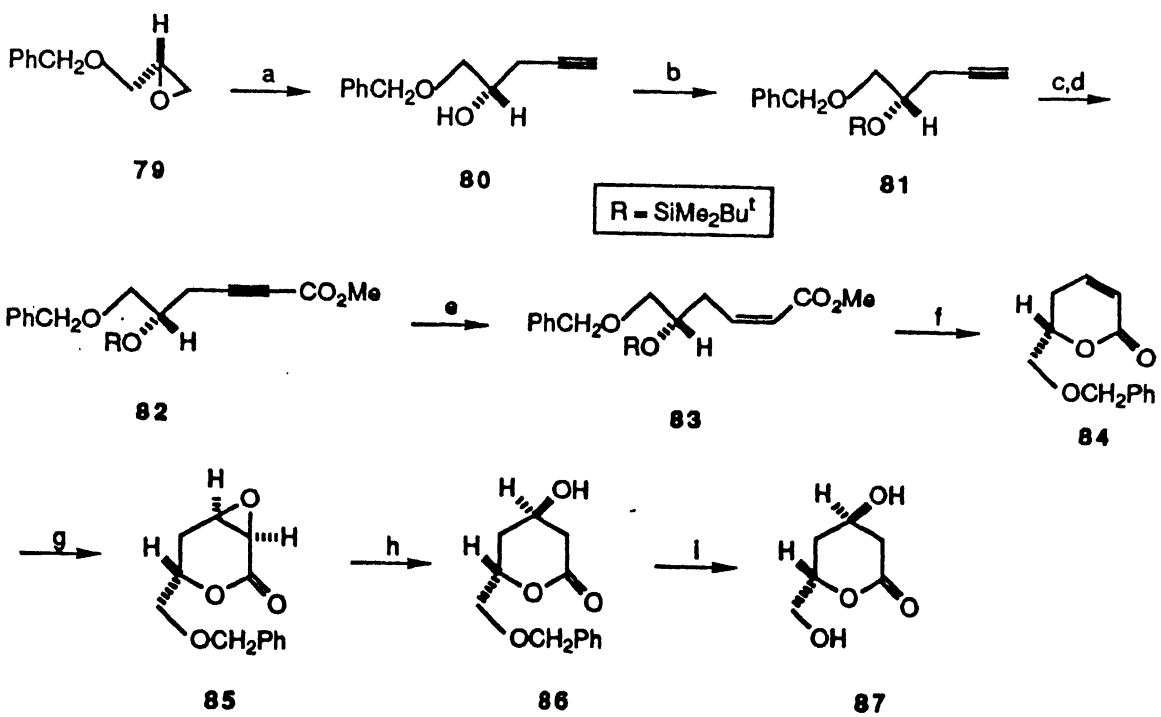


(a) $Bu^t Me_2SiOTf$, lutidine, CH_2Cl_2 (b) KOH, MeOH (c) PDC, CH_2Cl_2; 83% for steps a, b & c (d) Cat MeCu, Dibal-H, HMPA, - 50 °C, then at - 78 °C MeLi, TMSCl; 96% (e) O_3, MeOH, CH_2Cl_2, - 78 °C, then $NaBH_4$ followed by CH_2N_2; 89% (f) TsCl, Et_3N, DMAP (g) Ph_2CuLi, Et_2O (h) HF, CH_3CN; 78% for steps f, g & h (i) MnO_2

(R)-O-benzylglycidol **79** (Scheme 14). Treatment of **79** with sodium acetylide affords terminal acetylene **80**. Silyl protection of the OH function followed by sequential lithiation and methoxycarbonylation gives the ester **82**. Hydrogenation of **82** on Lindlar catalyst and brief exposure of the resulting olefin **83** to acid furnishes α,β-unsaturated lactone **84** with spontaneous desilylation and cyclization. Epoxidation of **84** with alkaline H_2O_2 proceeds stereoselectively to give epoxide **85**. Treatment of **85** with sodium phenylseleno(trisopropyloxy)borate ($NaBH_4$/PhSeSePh/AcOH-i-PrOH)[28] allows regioselective cleavage of the oxirane bond to furnish β-ketol **86**. Reductive removal of the benzyl group of **86** affords the lactone diol **87**.

A highly diastereoselective synthesis of the lactone portion **87** has been achieved by Jurczak and coworkers[29]. They make use

Scheme 14



79 **80** **81** **82** **83** **84** **85** **86** **87**

(a) NaH, DMSO, acetylene; 87% (b) $Bu^t Me_2SiCl$, imidazole; 99% (c) n-BuLi, THF, -72 °C (d) $ClCO_2Me$, -50 °C; 87% (e) H_2, PhH, Lindlar cat., quinoline, rt; 99% (f) conc HCl, MeOH, rt; 86% (g) 30% H_2O_2, 6N NaOH, MeOH, rt; 73% (h) $(PhSe)_2$, $NaBH_4$, AcOH, i-PrOH.

of the asymmetric hetero Diels-Alder reaction of 1-methoxybuta-1,3-diene **89** with (2R)-N-glyoxyloylbornane-10, 2-sultam **88** to furnish the adduct **90** (Scheme 15). Reduction of **90** followed by benzylation of hydroxy group affords **91**, which is subjected to anomeric oxidation[30] to produce **86**. Compound **86** is transformed into the pyrone **87** according to known procedure given by Takano and coworkers[27].

Knight and coworkers[31] have employed the (R)-hydroxy-ester **93** to architect chiral synthons for the elaboration to mevinic acids analogs utilising iodolactonization[32] and selenolactonization[33] under kinetic conditions as the key steps (Scheme 16).

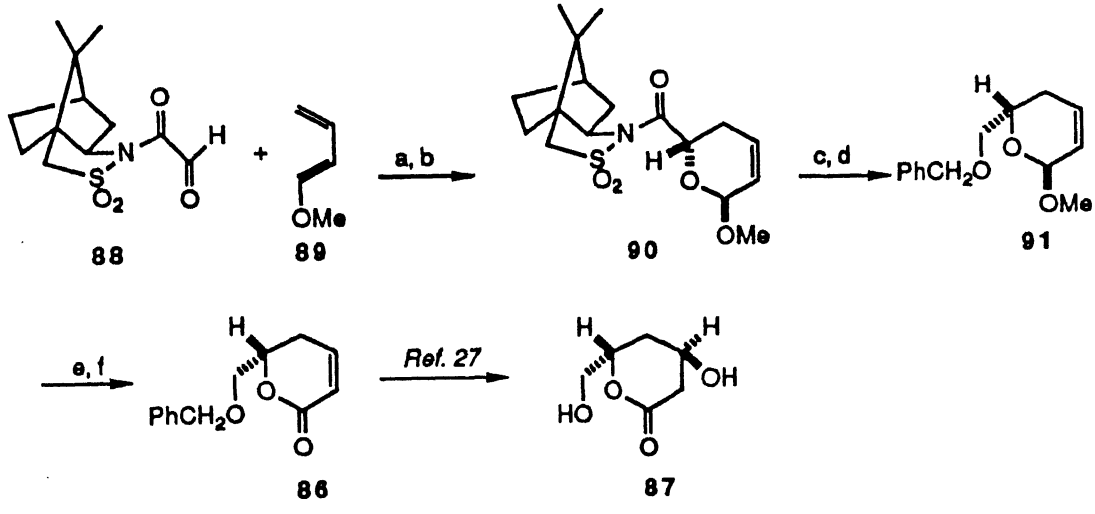
Path a: β-Hydroxy ester **93**, obtained by Baker's yeast reduction of β-ketoester **92**, is converted into silyl ether **94**. Treatment of the carboxylic acid derived from **94** with I_2 under kinetic conditions gives a 3:1 mixture of iodolactones **95** and **96**; **95** is purified by fractional recrystallization from pentane and transformed into mevinic acid analog **43P** via radical mediated coupling with β-tri-n-butylstannylstyrene. Treatment of iodolactone **95** with Na_2CO_3 gives 3(R),5(S)-epoxide **98**, which couples very efficiently with benzylic Grignard reagents in the presence of $CuBr.SMe_2$ to mevinic acid analogs[19,22].

Path b: Wittig homologation of the aldehyde **99**, obtained upon sequential treatment of silyl ether **94** with (a) ozone and dimethylsulfide, and (b) 2-phenylethylidene triphenylphosphorane, generated[34] by the addition of phenyllithium to vinyltriphenylphosphonium bromide (Schweizer's reagent), produces olefin **100** with 5:1 ***cis*** to ***trans*** ratio. Removal of silyl group of silyl ether **100** followed by saponification gives hydroxy acid,

which upon exposure to phenylselenenyl chloride affords selenolactones **101**. Selenolactones **101** are oxidised and during the process, selenoxides formed undergo elimination to afford 2:1 mixture of **43** and **43a** which subsequently proved to be readily separable by column chromatography.

Bonini and coworkers[35] have achieved a remarkably short synthesis of an optically active mevinic acid analog by

Scheme 15

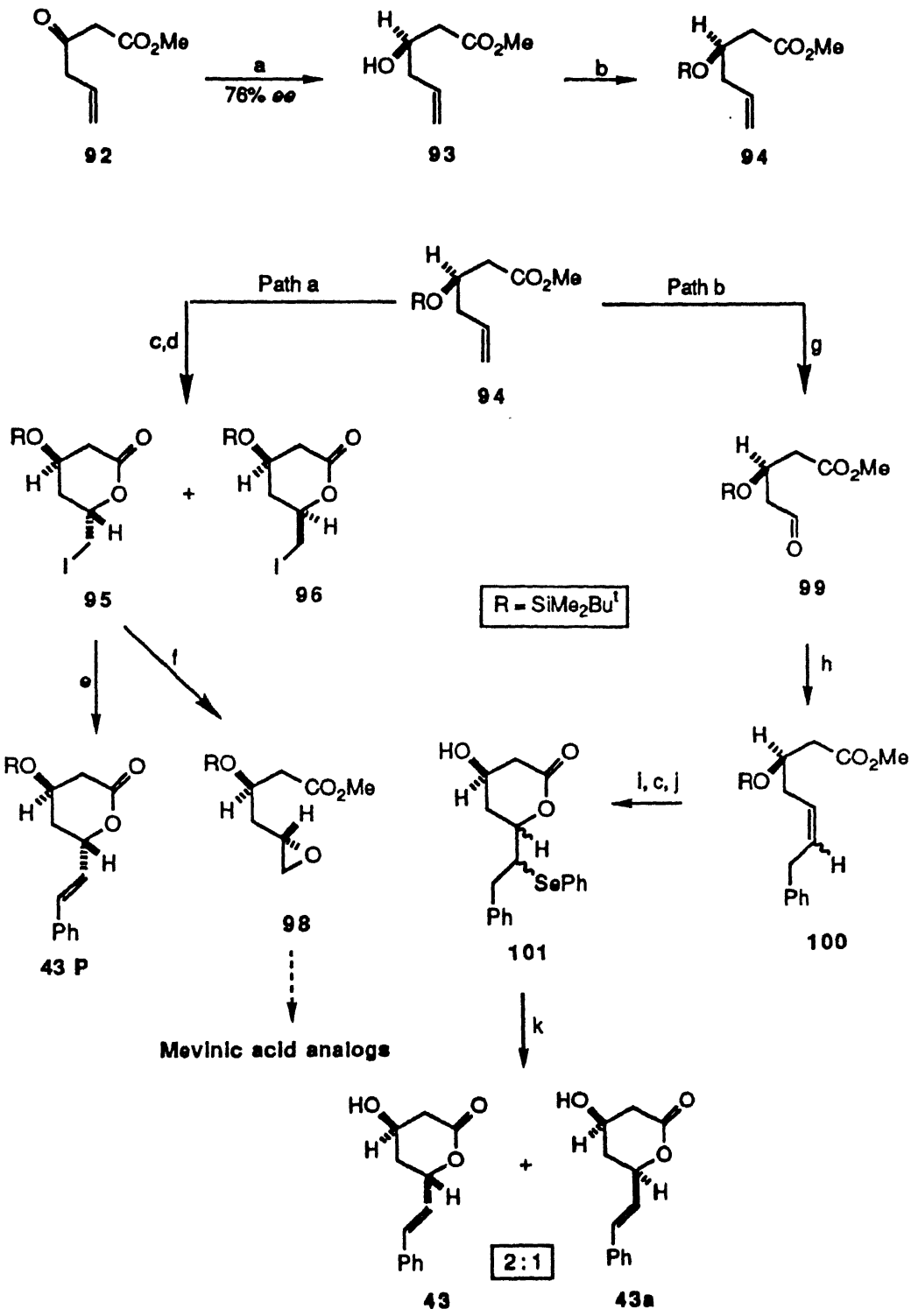


88 89 90 91 86 87

(a) 2 mol % Eu (fod)$_3$ (b) PPTS (c) $LiAlH_4$ (d) NaH, $PhCH_2Br$
(e) 30% H_2O_2, MoO_3 (cat) (f) Ac_2O, Pyridine

Eu (fod)$_3$ = [tris (6,6,7,7,8,8,8- heptafluoro- 2,2-dimethyloctane-3,5-dionato) europium (III)]
PPTS = pyridinium *p*-tolunesulfonate

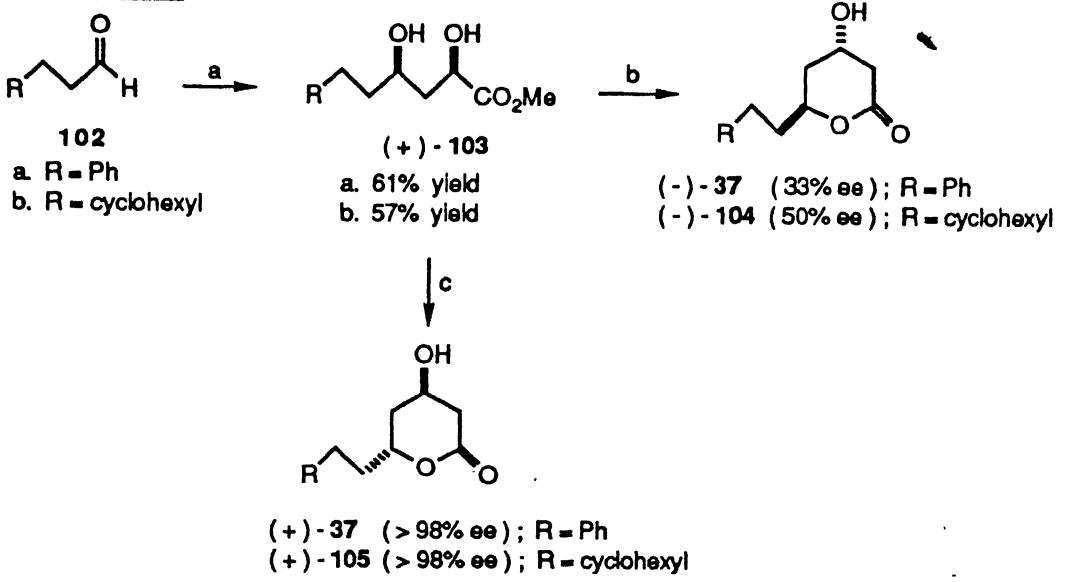
biocatalytic lactonization of *syn*-3,5-dihydroxy esters **103** (Scheme 17), which can be obtained by the diastereoselective reduction of the aldol derived from direct aldol condensation of the dianion of acetoacetate with an appropriate aldehyde **102**. Biocatalytic lactonization of **103 a/b** with pig liver esterase (PLE) affords unnatural mevinic acids analogs (-)-**37** and (-)-**104** respectively. But, when procine pancreatic lipase (PPL) is used to perform



(a) Baker's yeast ; 70% (b) $Bu^t Me_2SiCl$, imidazole, DMF; 75% (c) 2M NaOH (d) I_2, $NaHCO_3$, CH_3CN; 82% for steps c & d (e) $PhCH{=}CHSnBu_3$, AIBN, toluene ; 40% (f) Na_2CO_3, MeOH ; 90% (g) O_3, CH_2Cl_2, - 78 °C, then Me_2S ; 94% (h) $H_2C{=}CHPPh_3Br$, PhLi, THF ; 67% (i) 40% aq HF, CH_3CN (j) PhSeCl, THF, - 78 to 20 °C ; 50% for steps i, c & j (k) $NaIO_4$, THF : MeOH : H_2O (2 : 2 : 1) ; 63%.

lactonization of dihydroxy esters **103a/b**, natural analogs of mevinic acids (+)-**37** and (+)-**105** are obtained in good yield with high enantiomeric excess (ee).

Scheme 17



102
a. R = Ph
b. R = cyclohexyl

(+)-103
a. 61% yield
b. 57% yield

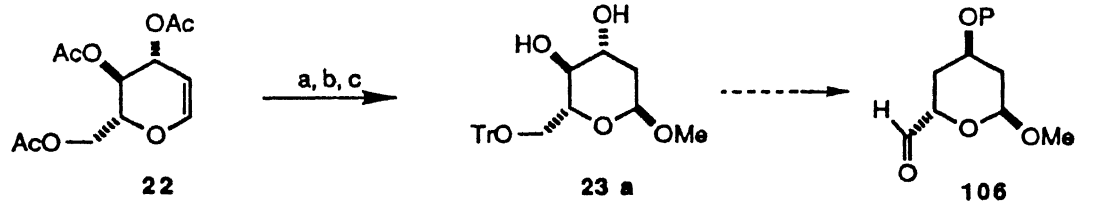
(-)-37 (33% ee); R = Ph
(-)-104 (50% ee); R = cyclohexyl

(+)-37 (>98% ee); R = Ph
(+)-105 (>98% ee); R = cyclohexyl

(a) 1. $H_3CCOCH_2CO_2Me$, 2 LDA 2. $Ti(OPr^i)_4$, $NaBH_4$ (b) PLE; 80% (c) PPL; 70%.

Newton and Pitchen and coworkers[36] have described a straightforward synthesis of the synthon **23a** from triacetoxy

Scheme 18



22

23 a

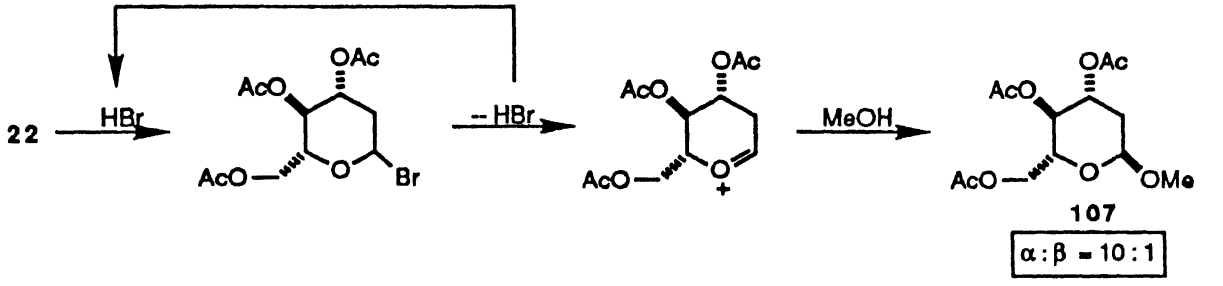
106

(a) MeOH, TBHP, DME (b) cat. NaOMe, rt (c) NEt_3, TrCl
65% yield for three steps

glucal **22** which has earlier been used by Yang and Falck[16] (Scheme 18). Glucal **22**, on reaction with MeOH in the presence of triphenylphosphine hydrobromide (TPHB) followed by sequential treatment with catalytic NaOMe and tritylation, affords **23a** as an

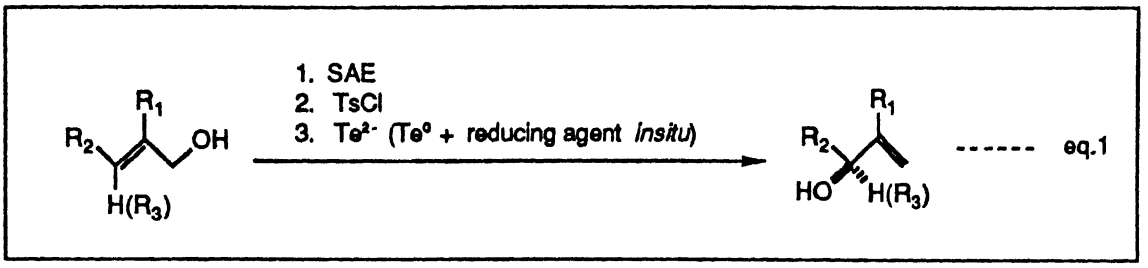
enantiomerically and diastereomerically pure product ($\alpha:\beta$ > 30:1).

Scheme 19

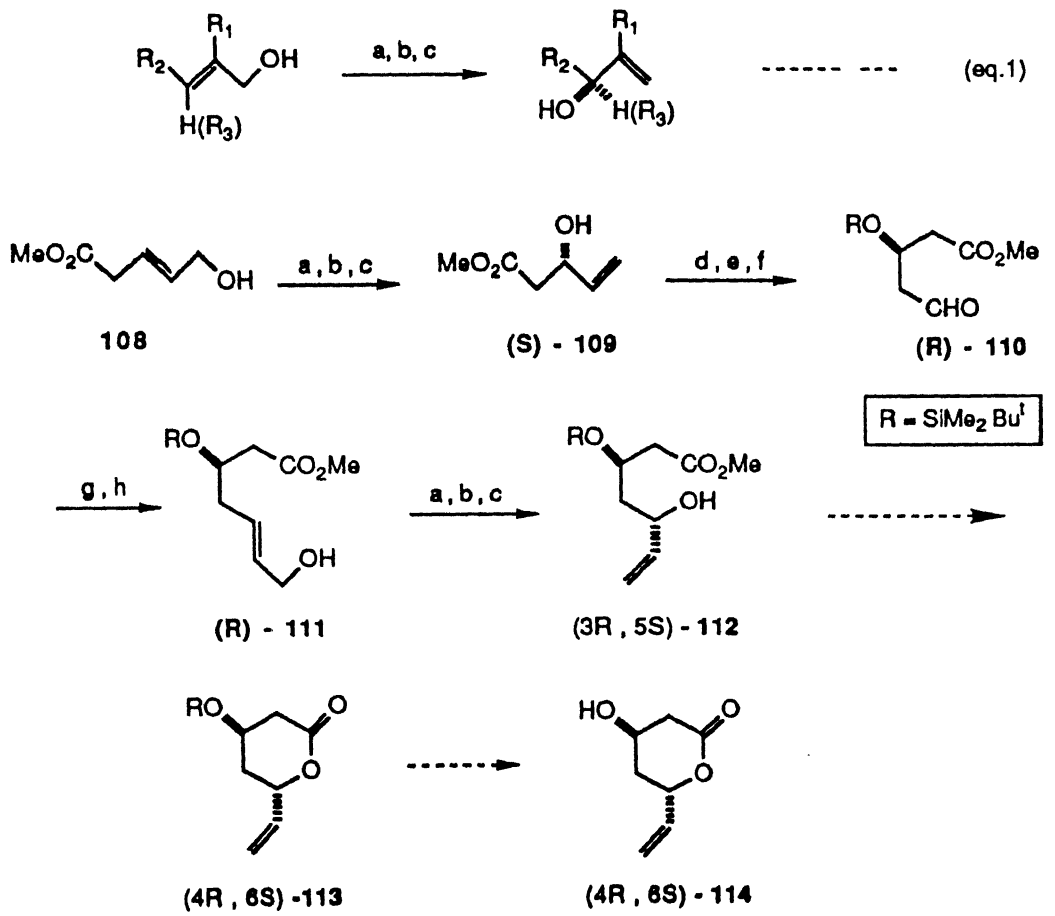


The transformation of **23a** into the lactone portion **106** can be performed according to the literature[16]. Authors hypothesise that HBr released from TPHB catalyses the addition of MeOH to **22** and TPHB only acts as a 'carrier' in the reaction. The major product **107** is also the α-anomer with no Ferrier rearranged product suggests the formation of an oxonium ion intermediate followed by addition of methanol (Scheme 19).

Dittmer and Kumar[37] have constructed the precursor **113** and transformed this into the lactone ring system **114** utilising the tellurium-induced nucleophilic reduction[38] in conjunction with the Sharpless asymmetric epoxidation (SAE) (eq 1). Scheme 20 depicts the overall process for the construction of **113**. The synthesis incorporates two telluride-induced transposition steps that preserve the stereochemistry introduced by SAE. The β,γ-unsaturated-δ-hydroxy ester **108** delivers, upon exposure to SAE followed by tosylation of hydroxy group, a glycidyl sulfonate, which is treated with telluride ion (Te^{2-}), produced *insitu* from tellurium and a reducing agent, to afford β-hydroxy-ester **109**.



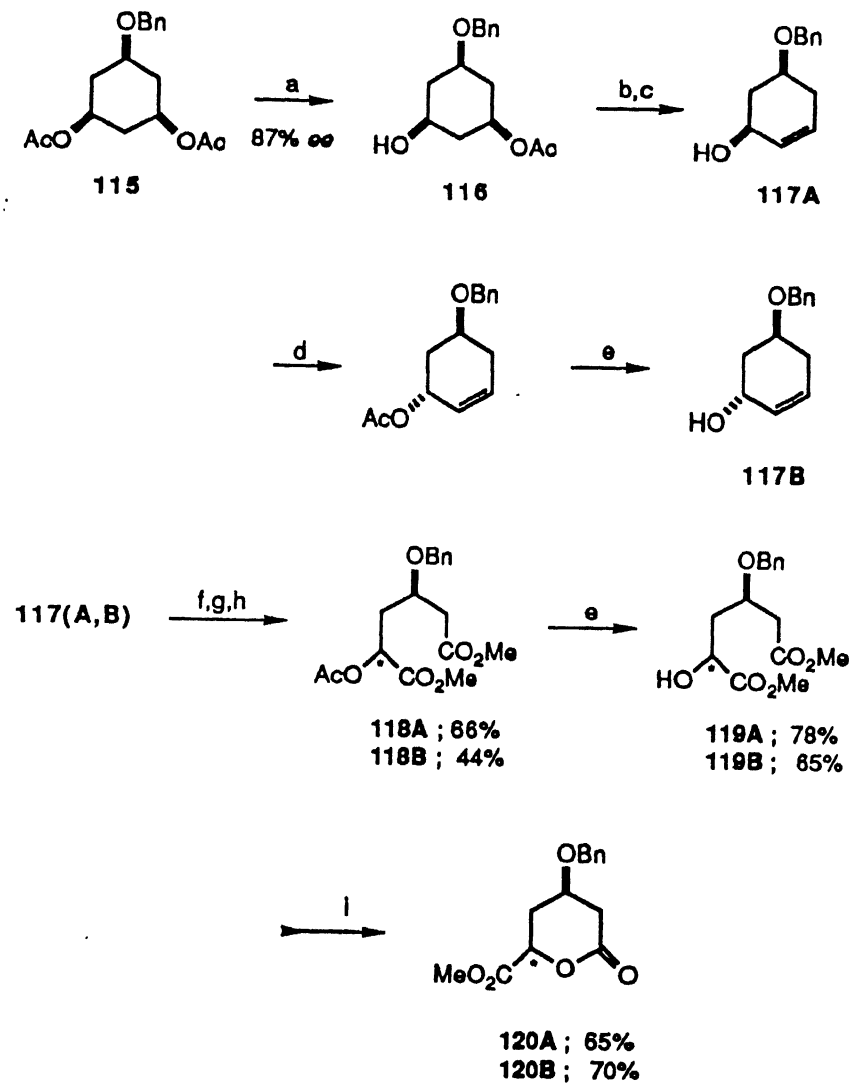
Scheme 20



(a) Bu^tO_2H, (+) - DIPT, Ti (O i-Pr)$_4$ (b) TsCl, Et_3N, CH_2Cl_2 (c) Te^{2-} (Te, $NaBH_4$, DMF)
(d) Bu^tMe_3SiCl, Imidazole, DMF (e) ($Me_2CH\,CHMe)_2BH$, THF, - 12 °C (f) PCC, CH_2Cl_2; 62% for steps d, e & f (g) $Ph_3P = CHCHO$, C_6H_6 /THF (h) $NaBH_4$, MeOH, - 50 °C; 60% for steps g & h.

Aldehyde **110** is acquired from **109** by functional group manipulations and submitted sequentially for Wittig reaction and borohydride reduction to furnish allyl alcohol **111**. SAE-Te transposition sequence on **111** gives monoprotected β,δ-dihydroxy ester **112** which, during the process, undergoes spontaneous lactonization to afford **113**.

Scheme 21



(a) PLE, pH 7.0 ; 62% (b) Swern oxidn. ; 92% (c) $NaBH_4$, $CeCl_3$, MeOH ; 90%
(d) PPh_3, DEAD, AcOH, THF ; 87% (e) K_2CO_3, MeOH ; 82% (f) O_3
(g) Jones oxidn (h) CH_2N_2 (i) pTSA, PhH

In a significant strategic departure Suemune, Matsuno, Uchida and Sakai[40] have used cyclohexanetriol derivative to construct compactin lactone moiety. Procine liver esterase (PLE) is applied to achieve enantioselection of **115** in the form of **116** (Scheme 21). Swern oxidation and subsequent stereoselective reduction by $NaBH_4$ in the presence of Ce^{3+} salts affords **117A**. Application of Mitsunobo's inversion reaction[41] on **117A** followed by ester hydrolysis gives epimeric material **117B**. The materials **117A** and **117B** are transformed into compactin lactone moiety **120A** and its C-6 epimer **120B**, respectively as per the sequence given.

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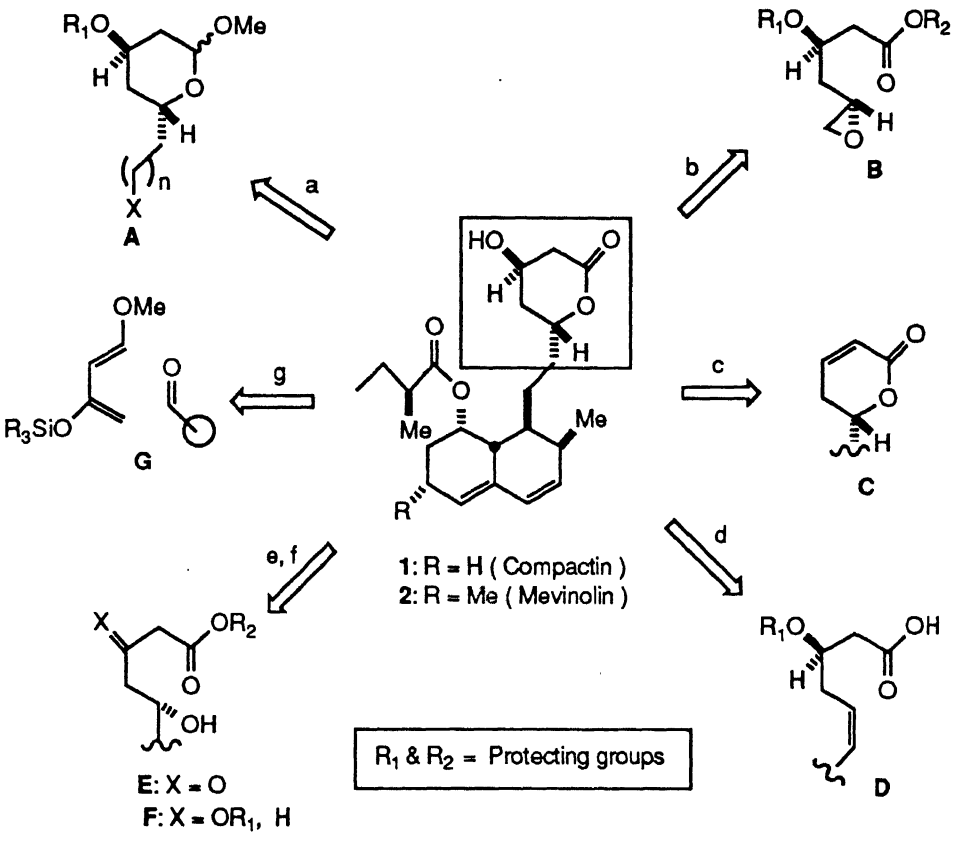
5-OXO-2-PHENYL-1,3-DIOXAN AND ITS DERIVATIVES AS PRECURSORS FOR SYNTHESIS OF MEVINIC ACID ANALOGS

2.0 Results and Discussion

Various synthetic endeavours aimed at the synthesis of key pharmacophore β-hydroxy-δ-lactone segment of mevinic acids described in the literature can be categorised into six types as depicted in Scheme 2.1. A commonly used strategy for the

Scheme 2.1

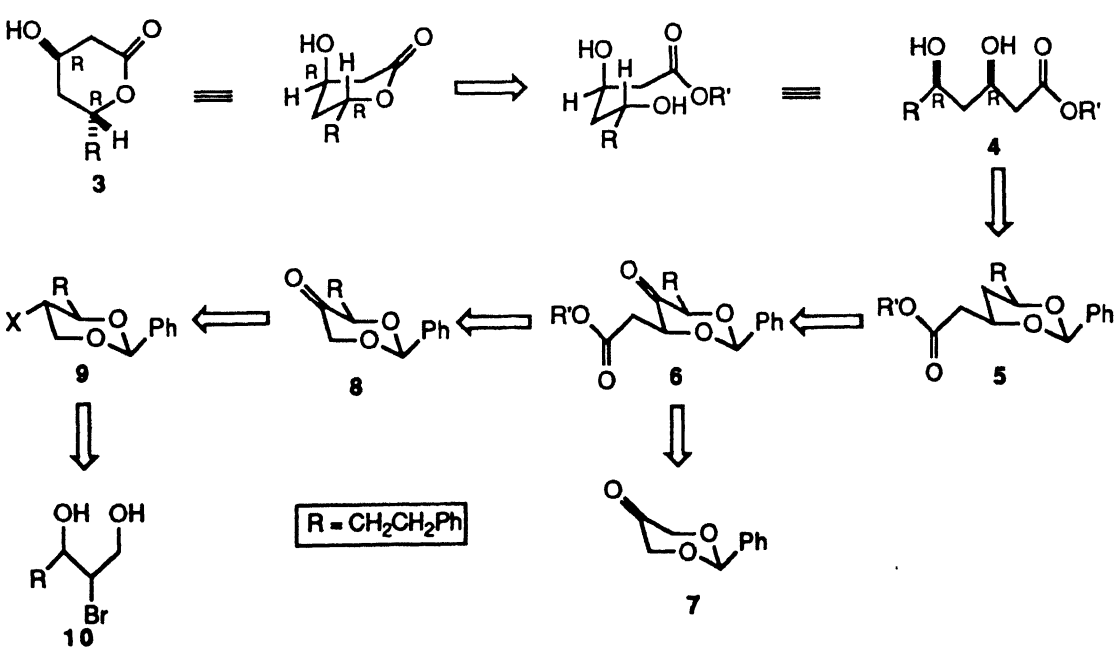


incorporation of the lactone portion in the synthesis of both the natural materials and the synthetic analogs is to employ the masked lactol **A** as an electrophilic species (Path a). This type of analog has often been obtained from carbohydrate degradation[1-4] as well as from L-malic acid[5,6]. Path b which leads directly to the mevinic acids as well as synthetic analogs involves the extremely efficient coupling of aryl cuprates with

chiral epoxy esters **B** which can be obtained from a variety of precursors[6]. In the third approach c, epoxidation of α,β-unsaturated lactones of type **C** followed by regioselective rupture of the oxirane ring leads to the β-hydroxy adorned lactone fragment[7]. The approach d embraces kinetically controlled iodolactonization and selenolactonization strategies to architect mevinic acid analogs[8]. Other viable open chain precursors of lactone moiety are of type **E** and **F**, which have been generated in optically active forms using chiral starting materials[9], chiral auxilliaries[10,11], and also enzymatic biocalatyses[12,13]. Chiral as well as racemic analogs have also been produced using a hetero Diels-Alder reaction[14,15] as the key step (Path g).

A close scrutiny of the precursor **F** (R_1= H) for the lactone function of mevinic acids suggests that other than the above

Scheme 2.2

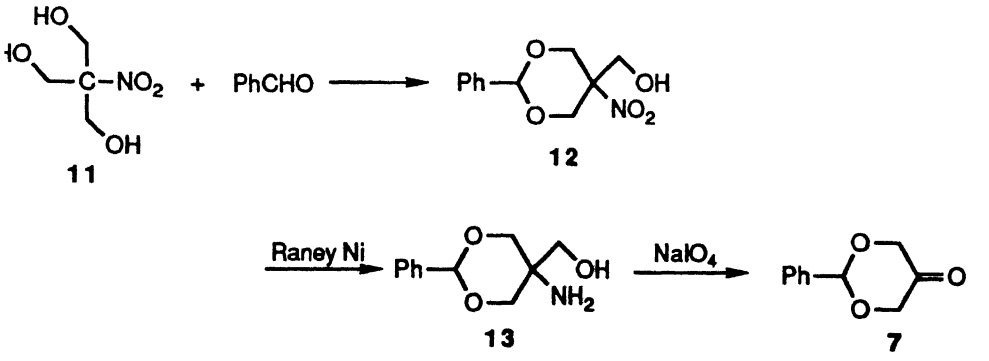


mentioned approaches, possibilities exist of its construction from benzylidene glycerol-like substrates. Retrosynthetic analysis of the lactone segment based on this analysis is shown in Scheme 2.2

We became interested to explore these possibilities. For the sake of convenience and simplicity, we replaced the substituent R by 2-phenylethyl function. The β,δ-dihydroxy ester **4** can be obtained from acetal cleavage in 2,4,6-trisubstituted-5-oxo-1,3-dioxan **6** following the lowering of the oxidation level of the carbonyl carbon to the level of a methylene function. Compound **6** can be made available from either the bisalkylation of 5-oxo-2-phenyl-1,3-dioxan **7** or the Kornblum oxidation of 2,4-disubstituted-5-bromo-1,3-dioxan **9** followed by monoalkylation.

Literature survey revealed that the compound **7** is readily available from tri(hydroxymethyl)nitromethane (Scheme 2.3) using Marei and Raphael protocol[16]. Condensation of tri(hydroxymethyl)-nitromethane **11** with benzaldehyde and catalytic reduction of the

Scheme 2.3



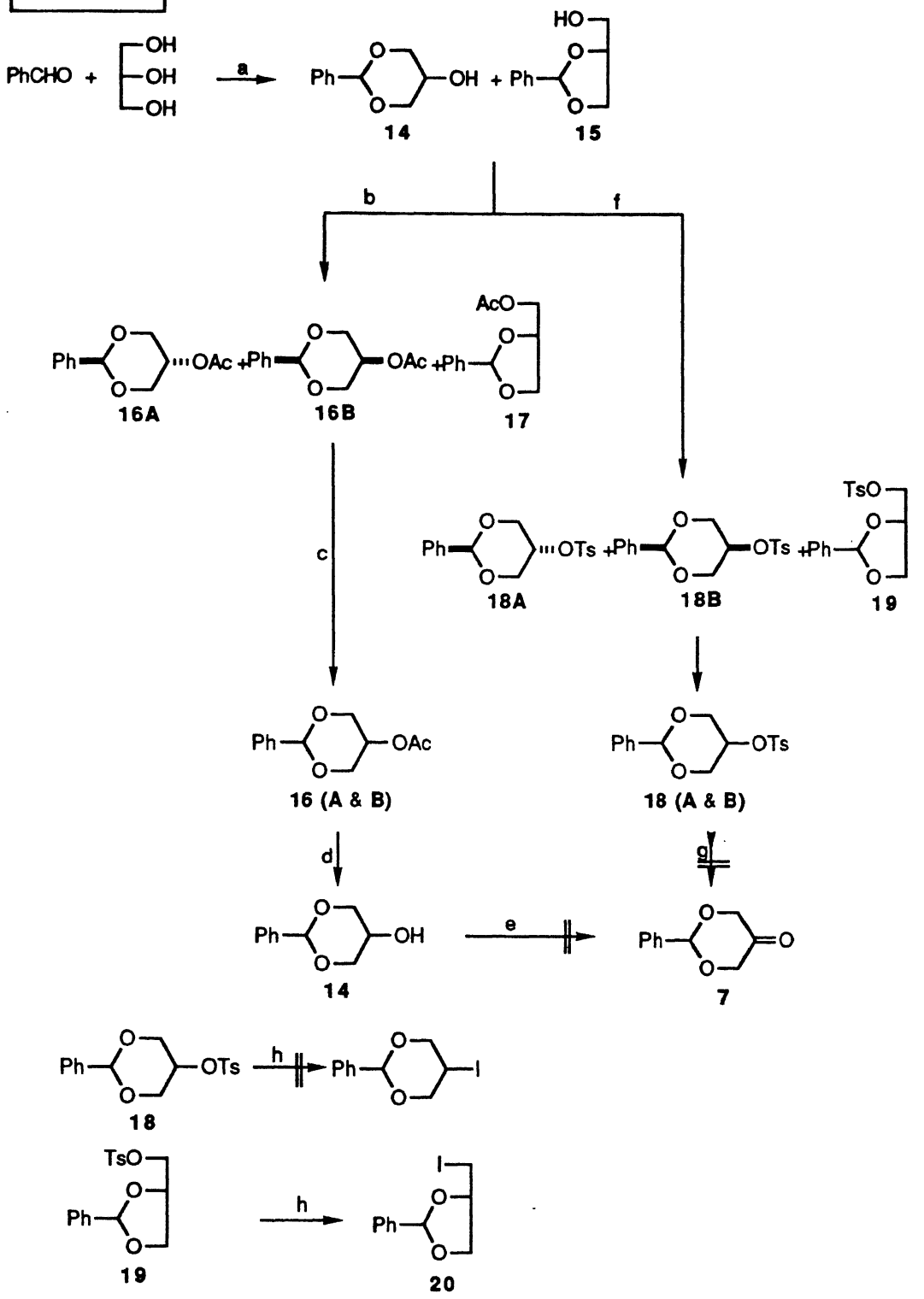
product with Raney nickel under 100 atmosphere of hydrogen at 80 ^{o}C for 4h furnished 5-amino-5-hydroxymethyl-2-phenyl-1,3-dioxan **13**. Fission of vicinal aminoalcohol **13** with sodium periodate

yields 5-oxo-2-phenyl-1,3-dioxan. Non-availability of facilities for conducting high pressure reactions prevented us to use this protocol. We sought to look for alternative methods for the synthesis of **7**. To this end, oxidation of benzylidene glycerol was considered a smart choice.

Following the protocol of Takano and coworkers[17], the condensation of glycerol and benzaldehyde in refluxing benzene in presence of catalytic amount of *p*-toluenesulfonic acid (p-TSA) with azeotropic removal of water furnished 5-hydroxy-2-phenyl-1,3-dioxan **14** and 4-(hydroxymethyl)-2-phenyl-1, 3-dioxolane **15** as an inseparable 1:1 mixture of two pairs of diastereoisomers.

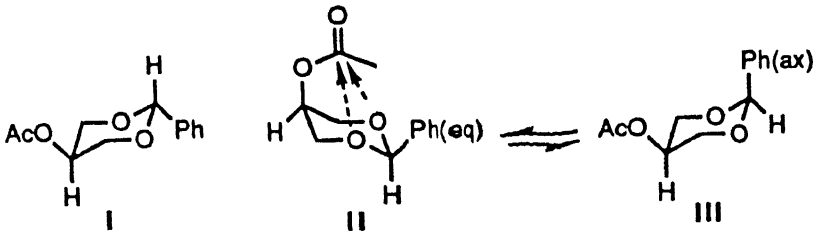
To accomplish the separation of the above alcohols, these were transformed into their corresponding acetates. The TLC of the reaction mixture on elution with 15% ethyl acetate in petroleum ether showed three distinct spots having R_f values: 0.5, 0.4 and 0.35. These spots were isolated by silica gel chromatography. The material with R_f value 0.5 i.e. **16A** (mp 107 - 109 ^{o}C) shows up in its ^{1}H NMR spectrum (Fig. 2.2) only one singlet at ppm 5.3 corresponding to acetal proton thereby revealing it to be a single isomer. Also, the presence of two sets of resonances at ppm 4.3 (dd, 2H, J = 10 and 5 Hz) and 3.5 (dd, 2H, J = 10 and 8.5 Hz) due to the C_4 and C_6 equatorial and axial-hydrogens, respectively, indicates **16A** to be *trans* 6-membered isomer. The compound with R_f value 0.35 i.e. **16B** (mp 93 - 95 ^{o}C) is also a single isomer because its ^{1}H NMR spectrum (Fig. 2.3) shows the presence of only one singlet at ppm 5.35 assigned to acetal-H and only one multiplet at ppm 4.05 due to

Scheme 2.4



(a) p-TSA, benzene, reflux, $-H_2O$ (azeotropically); 40% (b) Ac_2O, pyridine, CH_2Cl_2; 74% (c) Chromatographic separation on silica gel (d) NaOH, EtOH, quantitative (e) PCC or Swern oxidn; no reaction (f) TsCl, pyridine, CH_2Cl_2; 62% (g) Kornblum oxidn; no reaction (h) NaI, 2-butanone, reflux; 88%

both the C_4 and C_6 equatorial and axial hydrogens. IR (1725 cm^{-1} for **16A** and 1720 cm^{-1} for **16B**) and elemental analyses also support the structure assigned to **16A** and **16B**. The formulations of **16A** and **16B** are in accord with the literature[18]. *Trans* 5-acetoxy-2-phenyl-1,3-dioxan shows, in its ^1H NMR spectrum, a coupling pattern suggesting a rigid molecule of chair form with both the bulky groups equatorial as in I; the *cis* isomer exhibits a spectrum with only one multiplet for all C_4 and C_6 protons, suggesting that they have lost their axial and equatorial characteristics, and that the compound is an equilibrium mixture of two conformations, II and III, as shown below. The material



with R_f value 0.4 i.e. **17** is a 1:1 mixture of *cis* and *trans* 5-membered acetates because its ^1H NMR spectrum (Fig. 2.4) shows two singlets at ppm 5.8 and 5.6 of almost equal intensity corresponding to *cis* and *trans* acetal-H, respectively. Other ^1H NMR resonances, IR (1730 cm^{-1}) and elemental analysis (cf expt.2.1.2) are in harmony with the structural identity of **17**. Acetate **16A** on treatment with ethanolic NaOH afforded *trans* 6-membered alcohol **14** which was characterized by spectral means (cf expt. 2.1.3).

Literature survey revealed that the oxidation of systems like **14** can be accomplished using silver picolinate[19]. We wished to explore the use of conventional oxidising agents like pyridinium chlorochromate (PCC) and Swern reagents. Unfortunately, oxidation of alcohol **14** with either PCC[21] or Swern reagents (DMSO in combination with either trifluoroacetic anhydride[22] or oxalyl chloride[23]) were unsuccessful and only intractable product mixtures were obtained.

We next considered the Kornblum reaction of tosylate of the 6-membered ring alcohol. Alcohols **14** and **15** on tosylation and chromatographic purification furnished three compounds **18A, 19** and **18B** with **18A** the least polar and **18B** the most polar spot on TLC. Keeping in mind the structural assignments of **16A, 17** and **16B** and based on the spectral data **18A** is identified as *trans* 6-membered ring tosylate, **17** as 5-membered tosylate (mixture of *cis* and *trans* with *cis* in major amounts) and **18B** as the *cis* 6-membered ring tosylate. The ^{1}H NMR spectra of **18A, 18B** and **19** are exhibited in Figs. 2.5, 2.6 and 2.7 respectively. It is, however, known in the literature the S_N2 attack on substrates like cyclohexyl iodide[24a] and 2-phenyl-5-tosyloxy-1,3-dioxan[24b] is not favored presumably owing to their fixed conformations. To further confirm the formulation of **18A, 18B** and **19**, they were reacted separately with NaI in refluxing 2-butanone (Finkelstein reaction). The 6-membered ring tosylates **18A** and **18B** behaved neutral. Addition of phase-transfer catalyst 18-crown-6 did not bring any change. The 5-membered tosylates, however, underwent smooth displacement to the iodide **20**, characterised by spectral means (cf expt. 2.1.6).

Transformation of alcohols **14** and **15** into their corresponding acetates and tosylate should not affect much the chemical shifts of acetal hydrogens. With this in mind, ^{1}H NMR spectrum of the mixture of alcohols **14** and **15** was matched with the ^{1}H NMR spectra of acetates **16(A,B)** and **17**, and tosylates **18(A,B)** and **19** in order to unravel the origin of various singlets due to acetal hydrogens in the region from ppm 5.8 to 5.2 in the spectrum of alcohols. Overlapping the spectra of alcohols and 5-membered acetates **17**, it became unambiguously clear that singlets at ppm 5.8 and 5.6 originate from 5-membered ring alcohols with the downfield singlet belonging to the *cis* isomer. With similar exercise of overlapping of various spectra the singlets at ppm 5.3 and 5.2 were assigned to the 6-membered ring alcohols, the downfield singlet, again, belonging to the *cis* isomer.

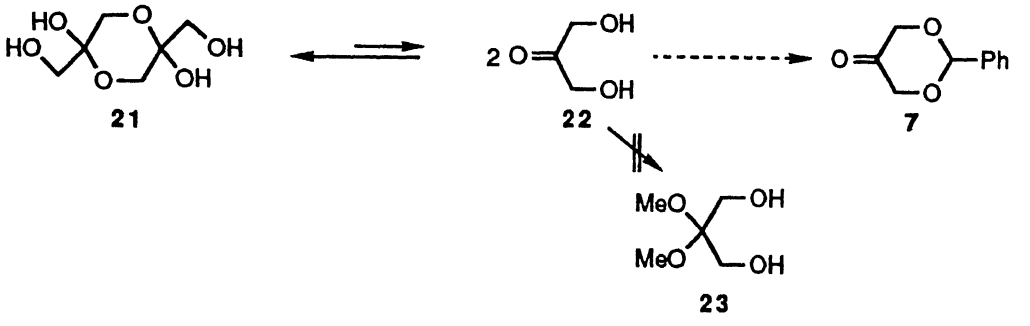
Kornblum reaction[25] of the 6-membered ring tosylate **18** with DMSO and $NaHCO_3$ at 100 ^oC for 4h led to the isolation of the starting tosylate with no oxidised product. In a bid to make the reaction mixture homogeneous, 2,4,6-collidine was employed in place of $NaHCO_3$. However, only the starting material was received. In parallel experiments where the temperature was raised to 150 ^oC, decomposition took place and only small amount of the starting material could be recovered.

Literature survey revealed that 1,3-dihydroxy acetone dimer, produced from glycerol by ***bacterium azetobacter*** under aerobic conditions is slowly soluble in H_2O and EtOH mixture (1:15). In freshly prepared solution, the dimer **21** reverts to monomer **22**[26].

We contemplated to trap the monomer 1,3-dihydroxy acetone to obtain the desired product **7** (Scheme 2.5). In this regard, a

solution of the dimer in MeOH:H_2O (15:1) was allowed to react with benzaldehyde and catalytic conc. HCl at reflux for 9h with azetropic removal of H_2O with MeOH. The reaction was unyielding. In another experiment, a solution of the dimer in MeOH and H_2O

Scheme 2.5

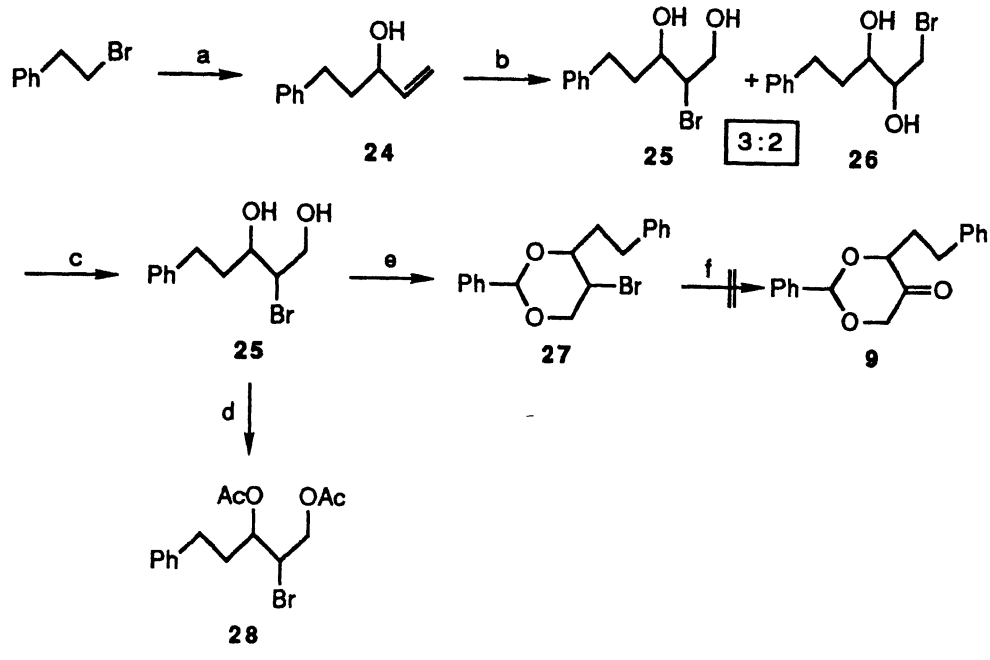


(15:1) was treated with excess benzaldehyde (10 equivalents) and fused $ZnCl_2$ (20 equivalents). Here, $ZnCl_2$ was expected to act as H_2O scavenger alongwith its usual capacity to function as a condensing agent; to our disappointment, no formation of the expected product was noticed.

In another series of experiments, it was decided to again make use of the Kornblum oxidation of bromide **27** to get 4-substituted 5-oxo-2-phenyl-1,3-dioxan **9**. Here, we were more hopeful of such a reaction taking place especially when performed in the presence of halophilic metal ions such as Ag^+. In order to prepare the requisite bromide **27**, we adopted the strategy shown in Scheme 2.6. The Grignard reagent derived from 2-bromoethylbenzene was reacted with acrolein resulting in the formation of the allyl alcohol **24**. Allyl alcohol **24** furnished, on treatment with N-bromosuccinamide (NBS) in wet DMSO, a mixture of the

bromohydrins **25** (m p 82 - 83 °C) and **26** (m p 58 - 59 °C) in the ratio ca 3:2. The structures of **25** and **26** were fully supported by

Scheme 2.6



(a) Mg, Et_2O, acrolein ; 89% (b) NBS-DMSO-H_2O; 82% (c) Chromatographic separation ; 52% (d) Ac_2O, pyridine, CH_2Cl_2 ; 86% (e) $PhCH(OMe)_2$, *p*-TSA, PhH, reflux ; 77% (f) Kornblum oxidn ; no reaction

spectral data and, more so, from further chemical transformations.

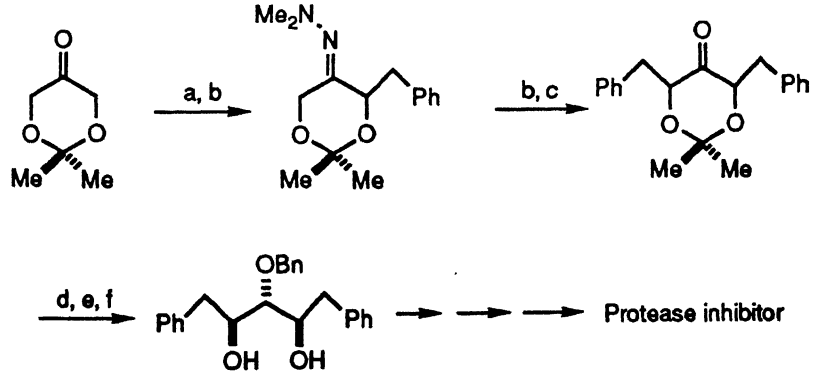
Condensation of bromodiol **25** with dimethyl acetal of benzaldehyde in presence of p-TSA in refluxing benzene with azeotropic removal of H_2O produced 5-bromo-2-phenyl-4-(2-phenyl-ethyl)-1,3-dioxan **27**. ^1H NMR (Fig. 2.8) signals at ppm 5.35 (s, 1H), 4.2 (bs, 2H), 4.0-3.8 (m, 1H) and 3.8-3.5 (m, 1H) are in consonance with the assigned structure **27**.

Kornblum oxidation[25] of bromoacetal **27** with DMSO and $NaHCO_3$ at 140 °C for 10 min resulted in a complex mixture (TLC). In

another bid, a mixture of the bromoacetal **27**, freshly prepared silver acetate[27], DMSO, and $NaHCO_3$ in dry acetonitrile were stirred overnight followed by heating to reflux for 5h under N_2 atmosphere. This experiment returned only the starting material **17**. Also, when silver acetate was replaced by freshly prepared silver tosylate[27], no reaction took place.

Finally, when we decided to use the known silver picolinate method[19] to achieve the requisite oxidation of benzylidene glycerol, a report by Enders and coworwers[28] appeared for the synthesis of C_2-symmetrical HIV-1 Protease Inhibitor (Scheme 2.7) in which the strategy employed by them is similar to what we had been trying to pursue. Consequent to this, our interest in above route was diminished and we took up alternative methods. This constitutes the subject matter for Chapter 3.

Scheme 2.7



(a) Me_2NNH_2, 65 °C (b) Bu^{t}Li, THF, -78 °C, $PhCH_2Br$, -95 °C (c) O_3, CH_2Cl_2, -78 °C; 44% for 4 steps (d) $LiAlH_4$, Et_2O, rt (e) NaH, $PhCH_2Br$, Bu_4NI, THF (f) 3N HCl, MeOH, rt; 53% for steps d, e & f.

2.1 Experimental

General Considerations: All experiments were performed in oven- or flame-dried glass apparatus. Reaction mixtures were magnetically stirred unless specified otherwise.

Melting points (m p) were determined in a Fischer-John melting point apparatus and are uncorrected.

Thin layer chromatography (TLC) was performed on prepared thin layers of either E-Merck silicagel G or Acme silicagel G (Bombay, India) on microslides. Visualization of spots was effected by ultraviolet illumination, exposure to I_2 vapours, 5% solution of 2,4-dinitrophenylhydrazine (DNP) in MeOH containing 10% (v/v) concentrated H_2SO_4, and spraying with 10% conc. H_2SO_4 in EtOH followed by charring on hot plate. Column chromatography was performed over silica gel (100-200 mesh) or neutral alumina using petroleum ether (60 - 80) and ethyl acetate mixtures as eluant.

Infrared (1R) spectra were recorded on Perkin Elmer 1320 spectrophotometer. Mass spectra were recorded on Jeol D-300 spectrometer at 70 eV. Proton magnetic resonance (^{1}H NMR) spectra were recorded on Bruker WP-80 ($CDCl_3$) or Varian EM-360L (CCl_4) series of spectrometers. ^{1}H chemical shifts are reported in parts per million (ppm) from tetramethylsilane (TMS) as internal standard. The abbreviations s,d,t,q, b and m in ^{1}H NMR spectra refer to singlet, doublet, triplet, quartet, broad and multiplet, respectively.

Ether, wherever used, stands for diethyl ether. All organic extracts were dried over anhydrous Na_2SO_4 and solvents were removed under reduced pressure on rotovap. Common abbreviations for solvents are used throughout, 0 ^oC stands for ice-H_2O slush

temperature; rt for room temperature, mix for mixture and aq for aqueous.

Elemental analyses were carried out by Coleman-Automatic Carbon, Hydrogen, Nitrogen and Sulphur analysers.

Commercial grade solvents were distilled before use. Solvents were dried as per established procedures[29].

2.1.1 Condensation of benzaldehyde and glycerol

A solution of glycerol (0.92 g, 10 mmol) and benzaldehyde (2.65 g, 25 mmol) in dry benzene (150 ml) was refluxed in presence of p-TSA (0.285 g, 1.5 mmol) with azeotropic removal of water using Dean-Stark apparatus. After 12h, the reaction mix was allowed to come to rt and poured slowly into saturated aq $NaHCO_3$ solution (40 ml) covered with ether (30 ml) under stirring and maintained at 5 - 10 ^{o}C. The layers were separated and the aq phase extracted with ether (2 x 40 ml). The combined organic solution was washed with H_2O (1 x 25 ml) and brine (1 x 30 ml). Drying, removal of volatiles, and chromatography over neutral alumina furnished 1:1 mix of 5-hydroxy-2-phenyl-1,3-dioxan **14** and 4-hydroxy methyl-2-phenyl-1,3-dioxolane **15**; 0.72 g (40%).

^{1}H NMR (60 MHz) : ppm 7.2 (s, 5H, Ar<u>H</u>), 5.8-5.2 [5.8(s), 5.6(s), 5.3(s), and 5.2(s), 1H, acetal-<u>H</u>], 4.3-3.1(m, 6H, 2xOC<u>H</u>$_2$, and -C<u>H</u>O<u>H</u>).

IR (Neat), ν_{max} : 3420 (OH), 1600, 1450, 1075 and 750 cm^{-1}.

2.1.2 Acetylation of alcohols 14 and 15

To a solution of the alcohols **14** and **15** (0.373 g, 2.07 mmol)

in dry dichloromethane (1 mL) was added dry pyridine (0.49g, 6.21 mmol) and one crystal of 4-dimethylaminopyridine (DMAP). The resultant solution was cooled to 0 ^{o}C and Ac_2O (0.42 g, 4.14 mmol) added dropwise (2 min). The reaction mix was allowed to come to rt and stirring continued for 4h. H_2O (2 ml) was added to the reaction mix, stirred for 30 min and transferred to a separatory funnel with the help of H_2O (4 ml) and dichloromethane (10 ml). The layers were separated and the aq phase extracted with dichloromethane (3 x 5 mL). The combined dichloromethane solution was washed rapidly with cold 2% aq HCl (1 x 5 ml), H_2O (1 x 5 ml), and brine (1 x 5 ml). Drying, removal of solvent, and chromatography of the residue over neutral alumina produced the *trans* 5-acetoxy-2-phenyl-1,3-dioxan **16A** (0.104 g, 23%), *cis* 5-acetoxy-2-phenyl-1,3-dioxan **16B** (0.08 g, 17%) and 1:1 *cis/trans* mix of 4-acetoxymethyl-2-phenyl-1,3-dioxolane **17** (0.157 g, 34%).

***Trans* 5-acetoxy-2-phenyl-1,3-dioxan 16A**

mp : 107 - 109 ^{o}C.

^{1}H NMR (60 MHz) : ppm 7.25 (s, 5H, Ar<u>H</u>), 5.3 (s, 1H, acetal-<u>H</u>), 5.2-4.5 (m, 1H, -<u>H</u>COAc), 4.3 (dd, 2H, J = 10 and 5 Hz, C_4 and C_6 equatorial-<u>H</u>), 3.5 (dd, 2H, J = 10 and 8.5 Hz, C_4 and C_6 axial-<u>H</u>), 2.0 (s, 3H, $-O_2CC\underline{H}_3$).

IR (KBr), ν_{max} : 1725 (acetate), 1375, 1240, 1100 and 750 cm^{-1}.

Analysis calcd.for $C_{14}H_{14}O_4$: C, 64.86, H, 6.30;
Found : C, 64.77, H, 6.49%.

Cis **5-acetoxy-2-phenyl-1,3-dioxan 16B**

m p : 93 - 95 ^{o}C.

^{1}H NMR (60 MHz) : ppm 7.4-7.0 (m, 5H, Ar$\underline{H}$), 5.35 (s, 1H, acetal-$\underline{H}$), 4.5 (m, 1H, -$\underline{H}$COAc), 4.05 (m, 4H, C_4 and C_6 equatorial and axial -$\underline{H}$), 2.1 (s, 3H, -$O_2CC\underline{H}_3$).

IR (KBr), ν_{max} : 1720 (acetate), 1240, 1135, 1080, 740 and 690 cm^{-1}.

Analysis calcd.for $C_{12}H_{14}O_4$: C, 64.86, H, 6.30;
Found : C, 64.95, H, 6.45%.

Cis/trans **4-acetoxymethyl-2-phenyl-1,3-dioxolane 17**

^{1}H NMR (60 MHz) : ppm 7.2 (s, 5H, Ar-$\underline{H}$), 5.9-5.5 [5.8(s) and 5.6(s), 1H, *cis* and *trans* acetal $\underline{H}$], 4.6-3.5 (m, 5H, -OC$\underline{H}$, -OC$\underline{H}_2$ and -$\underline{H}_2$COAc), 2.1-1.8 [2.0(s) and 1.9(s), 3H, -$O_2CC\underline{H}_3$].

IR (neat), ν_{max} : 1730 (acetate), 1310, 1230, 1100, 750 and 690 cm^{-1}.

Analysis calcd.for $C_{12}H_{14}O_4$: C, 64.86, H, 6.30;
Found : C, 64.93, H, 6.22%.

2.1.3 Hydrolysis of the acetate 16B (16B ⟶ 14)

2.5% ethanolic NaOH (4.8 ml, 3 mmol) was added to 5-acetoxy-2-phenyl-1,3-dioxane (0.222 g, 1 mmol) at 0 ^{o}C. The resultant mix is brought to rt and kept there for 20h. Ethanol was removed and the residue partitioned between ether (25 ml) and H_2O (10 ml). The layers were separated and the aq phase extracted with ether (2 x 25 ml). The combined ethereal extracts was successively washed with H_2O (1 x 15 ml) and brine (1 x 25 ml),

dried and concentrated. Chromatography over neutral alumina gave 0.18 g (quantitative) of *trans* 5-hydroxy-2-phenyl-1,3-dioxan **14**.

^{1}H NMR (80 MHz) : ppm 7.8-7.2 (bm, 5H, Ar-H), 5.5 (s, 1H, acetal-H), 3.5-3.3 (m, 6H, 2xOCH_2 and CHOH).

IR (neat), ν_{max} & : 3460(OH), 1600, 1310, 1150, 900 and 750 cm^{-1}.

2.1.4 Oxidation of 14

A. With PCC

Pyridinium chlorochromate (PCC, 0.323 g, 1.5 mmol), molecular seive type 4A (0.323 g), and freshly fused NaOAc (0.016 g, 0.2 mmol) were suspended in 2 ml of anhydrous dichloromethane and alcohol **14** (0.18 g, 1 mmol) solution in dichloromethane (2 ml) added in one portion under magnetic stirring. After 1.5 h, dry ether (5 ml) was added and the supernatent liquid decanted from a black gum. The insoluble residue was triturated with ether (3 x 5 ml). The solvents were removed and the residue after neutral alumina chromatography gave an intractable material.

B. With Swern's reagent

(i) DMSO-TFAA method: To a well stirred solution of dimethyl sulfoxide (0.156 g, 142 µl, 2 mmol) in dry dichloromethane (1 ml) at -60 ^oC was added trifluoroacetic anhydride (TFAA, 0.315g, 212 µl, 1.5 mmol) solution in dichloromethane (1 ml) over a period of 5 min when white precipitate formed. After 10 min a solution of the alcohol **14** (0.18 g, 1 mmol) in dichloromethane (0.5 ml) was added dropwise in 5 min. The resultant mix was stirred at -60 ^oC for 30 min followed by addition of triethylamine (0.4 ml). The reaction mix

was kept at -60 ^{o}C for a further 5 min and the cooling bath was removed to allow the reaction mix to come to rt (40 min). The volatiles were removed under reduced pressure on rotovap and the residue chromatographed over neutral alumina to give an intractable products mix.

(ii) DMSO-Oxalyl chloride method: The above experiment (2.1.4B.(i)) was repeated using oxalyl chloride in place of TFAA. After complete processing , unidentifiable products mix was obtained.

2.1.5 Tosylation of alcohols 14 and 15

Tosyl chloride (0.32 g, 1.66 mmol) was added portionwise (5 min) to a stirred solution of alcohols **14** and **15** (0.2 g, 1.11 mmol), pyridine (0.26 g, 3.33 mmol) and one crystal of DMAP in anhydrous dichloromethane (1 ml) at 0 - 5 ^{o}C. After complete addition, the reaction flask was well stoppered and kept in the regfrigerator (0 - 5 ^{o}C) overnight. H_2O (2 ml) was added to the reaction mix, stirred for 30 min and transferred to a separatory funnel with the help of ether (10 ml) and H_2O (4 ml). The aq layer was separated and extracted with ether (2 x 5 ml). Successive washing of the combined organic extracts with cold 2% aq HCl (1 x 4 ml), H_2O (1 x 4 ml) and brine (1 x 5 ml) gave a solution which was dried, concentrated and chromatographed over silica gel to furnish the *trans* 2-phenyl-5-tosyloxy-1,3-dioxan **18A** (0.073 g, 20%), *cis* 2-phenyl-5-tosyloxy-1,3-dioxan **18B** (0.057 g, 15%) and 2-phenyl-4-tosyloxymethyl-1,3-dioxolane **19** (0.102 g, 27%).

Trans **2-phenyl-5-tosyloxy-1,3-dioxan 18A**

^{1}H NMR (60 MHz) : 7.7 (d, 2H, J = 8 Hz, Ar-H *meta* to sulfonyl), 7.4-7.0 (m, 7H, Ar-H) 5.25 (s, 1H, acetal-H), 5.8 - 4.3 (m, 1H, -HCOTs), 4.3-4.0 (m, 2H, C_4 and C_6 equatorial-H), 3.9-3.4 (m, 2H, C_4 and C_6 axial-H), 2.4 (s, 3H, $ArCH_3$).

IR (neat), ν_{max} : 1590, 1450, 1360, 1170, 1100, 1000, 830 and 670 cm^{-1}.

Analysis calcd.for $C_{17}H_{18}O_5S$: C, 61.07, H, 5.38, S, 9.58;
Found : C, 61.13, H, 5.31, S, 9.44%.

Cis **2-phenyl-5-tosyloxy-1,3-dioxan 18B**

m p : 102 - 104 ^oC.

^{1}H NMR (60 MHz) : ppm 7.7 (d, 2H, J = 8 Hz, ArH, *meta* to sulfonyl), 7.3-7.0 (m, 7H, Ar-H), 5.45 (s, 1H, acetal-H), 4.5-4.2 (m, 1H, -HCOTs), 4.1-3.9 (m, 4H, C_4 and C_6 equatorial and axial-H), 2.4 (s, 3H, $ArCH_3$).

IR (KBr), ν_{max} : 1590, 1390, 1360, 1340, 1235, 1180, 1140, 1060, 950, 920, 890, 750, 730 and 650 cm^{-1}.

Analysis calcd.for $C_{17}H_{18}O_5S$: C, 61.07, H, 5.38, S, 9.58;
Found : C, 61.17, H, 5.43, S, 9.52%.

2-phenyl-4-tosyloxymethyl-1,3-dioxolane 19

^{1}H NMR (60 MHz) : ppm 7.8-7.0 (m, 9H, ArH), 5.7 (s, 1H, acetal-H), 4.5-3.5 (m, 5H, -OCH, $-OCH_2$, $-H_2COTs$), 2.4 (s, 3H, $ArCH_3$).

One singlet at ppm 5.6 present in ^{1}H NMR spectrum of 19 is due presumably to the other isomer.

IR (neat), ν_{max} : 1590, 1460, 1350, 1170, 1090, 960, 810, 750 and 660 cm^{-1}.

Analysis calcd.for $C_{17}H_{18}O_5S$: C, 61.07, H, 5.38, S, 9.58;
Found : C, 60.98, H, 5.43, S, 9.65%.

2.1.6 Finkelstein reaction of 5-membered tosylate 19

A mix of tosylate **19** (0.05 g, 0.15 mmol) and sodium iodide (0.067 g, 0.45 mmol) was refluxed in 2-butanone (3 ml) for 5h. Butanone was removed and the residue partitioned between ether (20 ml) and H_2O (10 ml). The layers were separated and the aq phase extracted with ether (2 x 10 ml). The combined ethereal extract was successively washed with cold 5% aq sodium thiosulfate solution (1 x 10 ml), H_2O (1 x 10 ml) and brine (1 x 10 ml). Drying, concentration and chromatography over neutral alumina gave 4-iodomethyl-2-phenyl-1,3-dioxolane **20** (0.038 g, 88%).

^{1}H NMR (60 MHz) : ppm 7.2 (s, 5H, Ar-H), 5.9 (s, 1H, acetal-H), 4.6-3.6 (m, 3H, OCH_2 and OCH), 3.4-2.9 (m, 2H,- H_2CI).

One singlet seen at 5.7 ppm in ^{1}H NMR spectrum of **20** *is due presumably to the other isomer.*

IR (neat), ν_{max} : 1590, 1460, 1250, 1040, 900, 840 and 770 cm^{-1}.

Mass (m/z) : 290 (M^+).

2.1.7 Kornblum oxidation of 6-membered tosylate 18 (A and B separately)

Method A : A mixture of 6-membered tosylate **18** (*cis* and *trans* separately; 0.05 g, 0.15 mmol) and $NaHCO_3$ (0.025 g, 0.3

mmol) in DMSO (0.4 ml) was heated, under N_2 atmosphere, to 95 - 100 ^oC for 4h. After allowing the reaction mix to come to rt, it was poured into 3 ml of cold H_2O and extracted with ether (3 x 10 ml). The combined ether extracts was washed with cold H_2O (2 x 5 ml) and brine (1 x 5 ml). Drying and evaporation of the solvents gave the starting material **18** only.

Method B: The above experiment was repeated using 2,4,6-collidine (0.018 g, 0.15 mmol) in place of $NaHCO_3$. This time also, only the starting tosylate **18** was recovered.

In parallel experiments where the temperature was raised to 150 ^oC for 4h, only decomposition was observed.

2.1.8 Grignard reaction of 2-bromoethyl benzene and acrolein

A flame-dried two necked round-bottom flask, equipped with a reflux condenser, magnetic stirrer and a dropping funnel was charged with magnesium turnings (1.296 g, 54 mmol atom), two crystals of I_2 and 5 ml of dry ether under N_2. A solution of 2-bromoethyl benzene (6.66 g, 4.93 ml, 36 mmol) in ether (20 ml) was taken in the dropping funnel and drained into the reaction flask at a rate so as to maintain a mild reflux. The addition took 30 min. After complete addition, the solution became hazy and most of the magnesium was dissolved. Stirring at rt was continued for a further 30 min and a solution of freshly distilled acrolein (1.68 g, 2.0 ml, 30 mmol) in ether (25 ml) was added dropwise over a period of 45 min under vigorous stirring. The resultant mix was refluxed for 1h, cooled to rt, and poured slowly into saturated aq NH_4Cl solution (20 ml) under stirring. The resultant biphasic solution was filtered off through a celite pad

to break the emulsion formed. The layers of the filterate were separated and the aq layer extracted with ether (3 x 25 ml). The combined organic solution was washed with H_2O (1 x 20 ml) and brine (1 x 25 ml). Drying, evaporation of the volatiles, and chromatography furnished the desired 3-hydroxy-5-phenyl-1-pentene **24** (4.36 g, 89%).

^{1}H NMR (60 MHz) : ppm 7.0 (s, 5H, Ar-H), 6.0-5.4 (m, 1H, -HC=CH_2), 5.3-4.7 (m, 2H, HC=CH_2), 3.9 (q, 1H, J = 6 Hz, -CHOH), 2.8-2.4 (m, 3H, OH and $PhCH_2$), 2.0-1.5 (m, 2H, $PhCH_2CH_2$).

IR (neat), ν_{max} : 3380 (OH), 1595, 1490, 1445, 910, 780, 750 and 690 cm^{-1}.

Mass (m/z) : 162 (M^+).

2.1.9 Formation of bromohydrins from alcohol 24

The above alcohol **24** (0.81 g, 5 mmol) was taken in 7 ml of DMSO and H_2O (4:1) and cooled to 0 ^oC.To it was added,portionwise, N-bromosuccinimide (NBS, 1.34 g, 7.5 mmol) over a period of 15 min. After 15 min the reaction mix was taken in ether (60 ml) and washed with cold H_2O (3 x 20 ml) and brine (1 x 20 ml). Drying, removal of solvents, and chromatography over silica gel gave 0.683 g (52%) of 2-bromo-5-phenyl-pentan-1,3-diol **25** and 0.39 g (30%) of 1-bromo-5-phenyl-2,3-diol **26**.

2-Bromo-5-phenyl-pentan-1,3-diol **25**

m p : 82 - 83 ^oC.

^{1}H NMR (80 MHz) : ppm 7.3-6.8 (m, 5H, Ar-H), 4.1-3.2 (m, 4H, -CH_2OH, CHBr, CHOH), 2.8-2.0 (m, 4H, $PHCH_2$,

and 2 x OH), 2.0-1.3 (m, 2H, $PhCH_2CH_2$).

IR (KBr), ν_{max} : 3310 (OH), 1590, 1490, 1440, 1030, 930, 740 and 690 cm^{-1}.

Mass (m/z) : 259 (M^+).

1-bromo-5-phenyl-2,3-diol **26**

m p : 58 - 59 ^oC.

^1H NMR (80 MHz) : ppm 7.8-7.3 (m, 5H, Ar-H), 3.9-3.2 (m, 4H, $CH_2BrCHOHCHOH$), 2.9-2.2 (m, 2H, $PhCH_2$), 2.1-1.2 (m, 4H, 2 x OH and $PhCH_2CHH_2$).

IR (KBr), ν_{max} : 3300 (OH), 1590, 1490, 1445, 1080, 940 and 770 cm^{-1}.

Mass (m/z) : 260 ($M^+ + 1$), 259 (M^+).

2.1.10 Acetylation of bromodiol 25

Acetylation experiment was conducted following the procedure as described in experiment 2.1.2 using the following ingradients.

Bromodiol **25** (0.015 g, 0.057 mmol), pyridine (4 drops), Ac_2O (2 drops) and one crystal of DMAP. Standard processing and chromatography afforded 0.017 g (86%) of diacetate **28**.

^1H NMR (60 MHz, $CDCl_3$) : ppm 7.0 (s, 5H, Ar-H), 5.1-4.7 (m, 1H, HCOAc), 4.3-3.7 (m, 3H, CHBr, CH_2OAc), 2.7-2.3 (m, 2H, $PhCH_2$), 2.1 (s, 3H, $-O_2CCH_3$), 2.0 (s, 3H, $-O_2CCH_3$), 2.2-1.5(m, 2H, $PhCH_2CH_2$).

IR (KBr), ν_{max} : 1720 (acetate), 1600, 1460, 950 and 760 cm^{-1}.

Analysis calcd.for $C_{15}H_{19}BrO_4$: C, 52.47, H, 5.54;
Found : C, 52.53, H, 5.46%.

2.1.11 Preparation of 5-bromo-2-phenyl-4-(2-phenylethyl)-1,3-dioxan 27

A mixture of bromodiol **25** (0.26 g, 1mmol), benzaldehyde dimethyl acetal (0.167 g, 1.1 mmol) and p-TSA (0.01 g, 0.06 mmol) was refluxed in dry benzene (10 ml) for 3h. This was diluted with ether (25 ml) and given successive washings with cold 10% aq $NaHCO_3$ solution (1 x 10 ml) and H_2O (1 x10 ml). Drying, evaporation of solvents, chromatography of the residue over neutral alumina gave bromoacetal **27** (0.26 g, 77%).

^{1}H NMR (60 MHz, $CDCl_3$) : ppm 7.6-6.9 (m, 10H, Ar-H), 5.35 (s, acetal-H), 4.2 (bs, 2H, OCH_2), 4.0-3.8 (m, 1H, methine OCH), 3.8-3.5 (m, 1H, CHBr), 2.7 (t, 2H, J = 8 Hz, $PhCH_2$), 2.4-1.3 (m, 2H, $PhCH_2CH_2$).

IR (neat), ν_{max} : 1600, 1320, 1120, 1030, 910 and 760 cm^{-1}.

Analysis calcd.for $C_{18}H_{19}BrO_2$: C, 62.24, H. 5.47;
Found : C, 62.36, H, 5.37%.

2.1.12 Kornblum Oxidation of Bromoacetal 27

Method A: A mixture of bromoacetal **27** (0.017 g, 0.05 mmol), freshly prepared silver acetate (0.01 g, 0.06 mmol), $NaHCO_3$ (0.03 g, 0.35 mmol), and anhydrous DMSO (1 ml) in anhydrous acetonitrile (2 ml) was stirred overnight followed by heating to reflux for 5h under N_2. The reaction mix was cooled to rt, acetonitrile removed and the residue partitioned between ether (10 ml) and cold H_2O (5

ml). The layers were separated and the aq phase extracted with ether (2 x 10 ml). The combined organic solution was washed with cold H_2O (3 x 15 ml) and brine (1 x 15 ml). Drying and evaporation of the solvents returned the starting bromoacetal **27** (0.016 g).

Method B: To a solution of freshly prepared silver tosylate (0.036 g, 0.13 mmol) in dry acetonitrile (2 ml) was added bromoacetal **27** (0.034 g, 0.01 mmol) and stirred for 30 min followed by addition of $NaHCO_3$ (0.06 g, 0.7 mmol) and anhydrous DMSO (1 ml). This was stirred overnight followed by reflux for 5h. Removal of acetonitrile gave a residue which was partitioned between ether (25 ml) and H_2O (5 ml). The aq layer was removed and the ether layer was washed with cold H_2O (4 x 5 ml) and brine (1 x 5 ml). Drying and removal of the solvents gave the starting material **27** (0.3 g).

Method C: A mixture of bromoacetal **27** (0.017 g, 0.05 mmol) and $NaHCO_3$ (0.03 g, 0.35 mmol) in anhydrous DMSO (0.5ml) was heated at 140 ^oC under N_2 for 10 min. The reaction mix was diluted with ether (20 ml) and washed with cold H_2O (4 x 5 ml) and brine (1 x 5 ml). Drying and solvent removal gave a complicated products mixture.

Method D: A solution of bromoacetal **27** (0.034 g, 0.1 mmol) in dry DMSO (0.25 ml) was injected into a suspension of $NaHCO_3$ (0.06 g, 0.7 mmol) in DMSO (1 ml) maintained at 140 ^oC. After 30 min the reaction mix was allowed to come to rt, diluted with ether (25 ml) and washed successively with cold H_2O (4 x 5 ml) and brine (1 x 5 ml). Drying and evaporation of solvent gave an intractable products mixture.

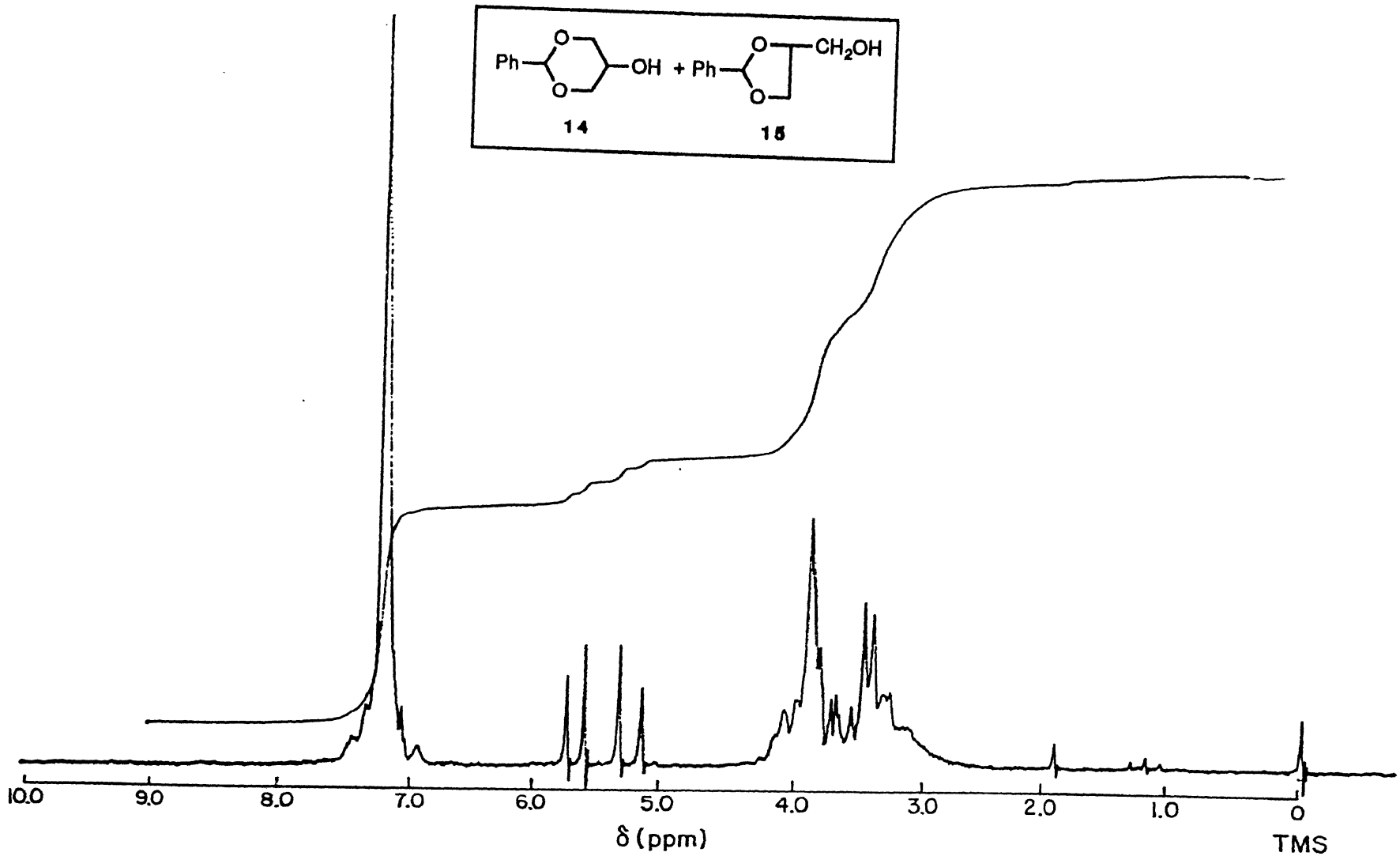


Fig. 2.1 ^{1}H NMR spectrum (60MHz)of **14** & **15**

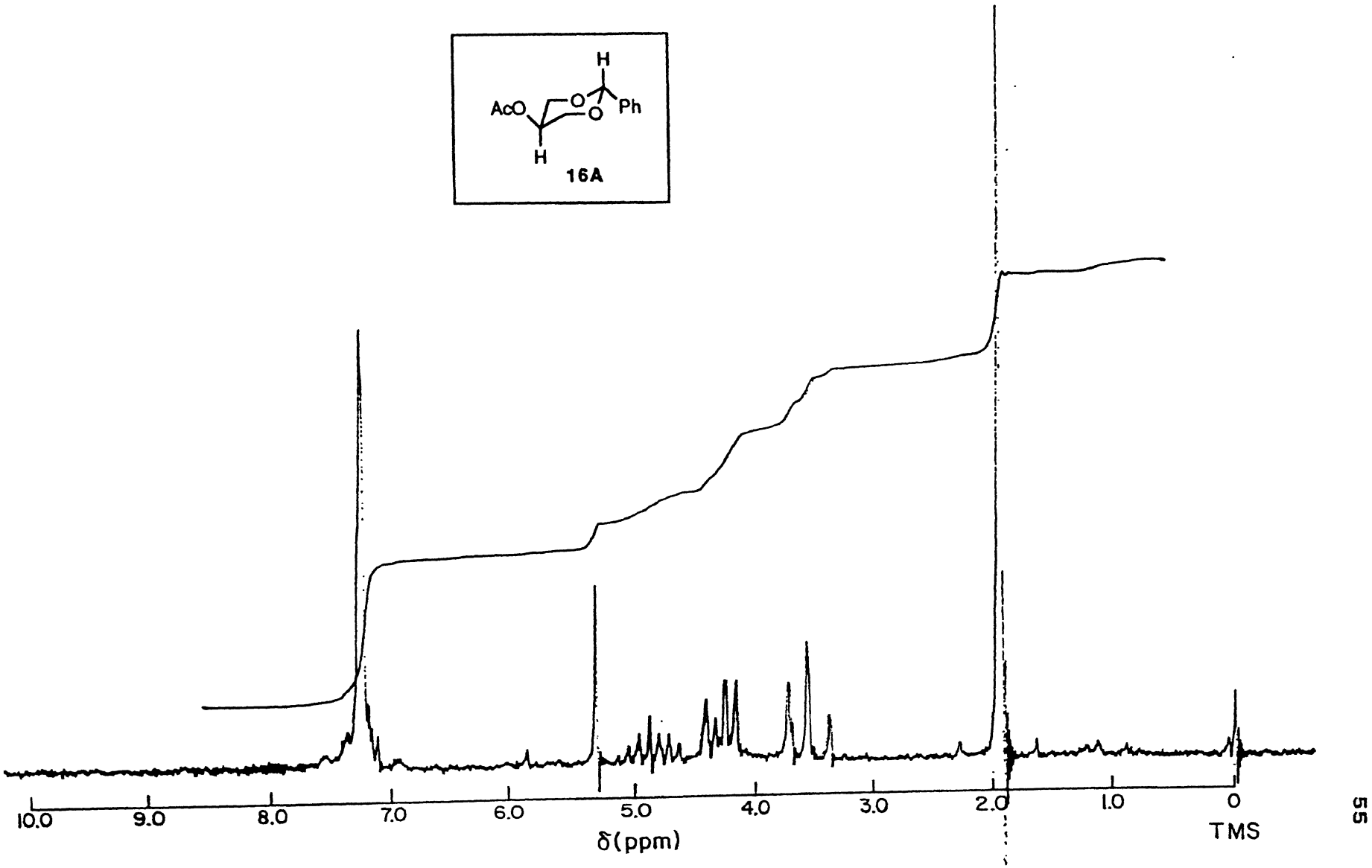


Fig. 2.2 ^{1}H NMR spectrum (60MHz)of **16A**

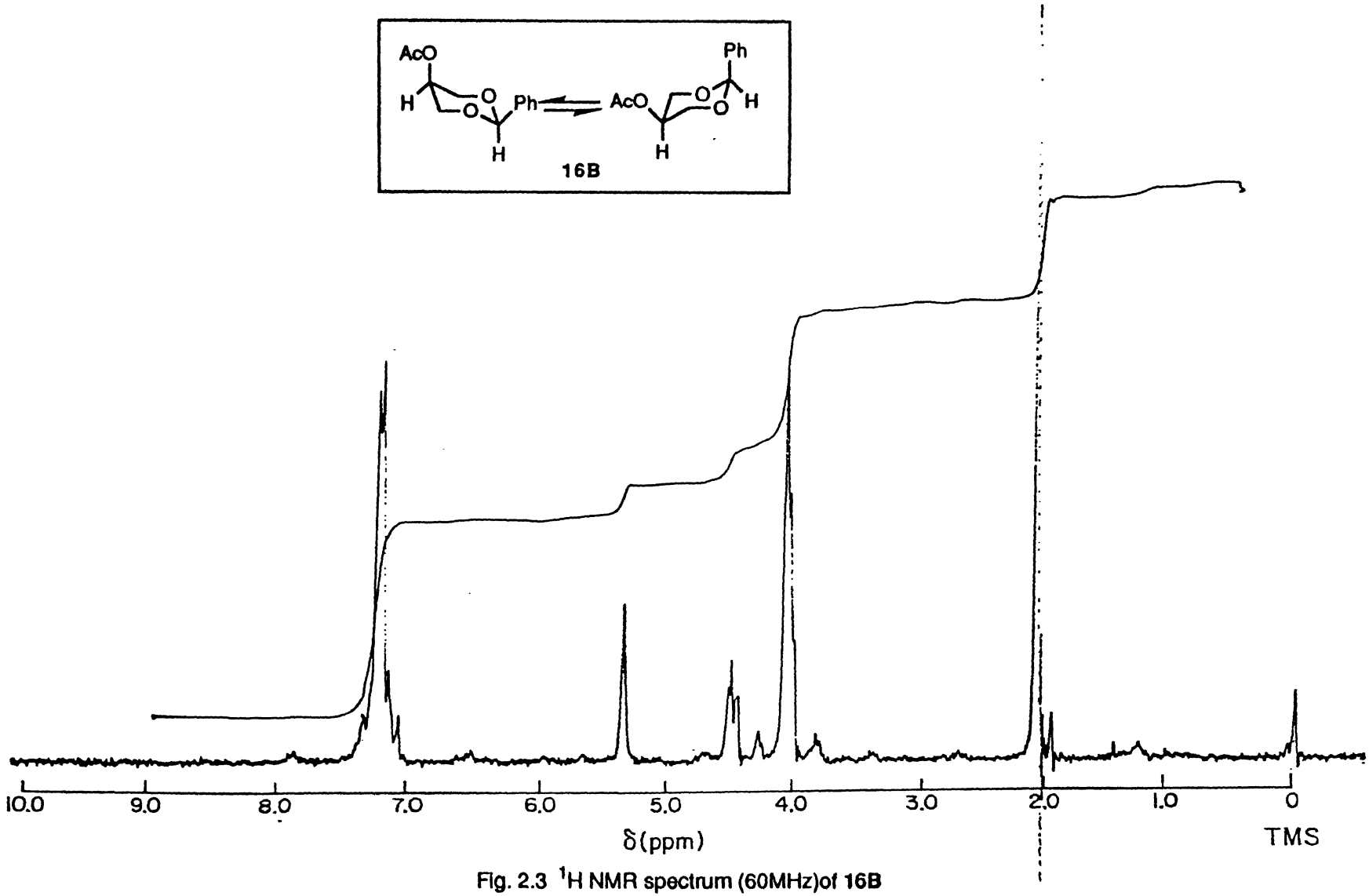


Fig. 2.3 ^{1}H NMR spectrum (60MHz)of **16B**

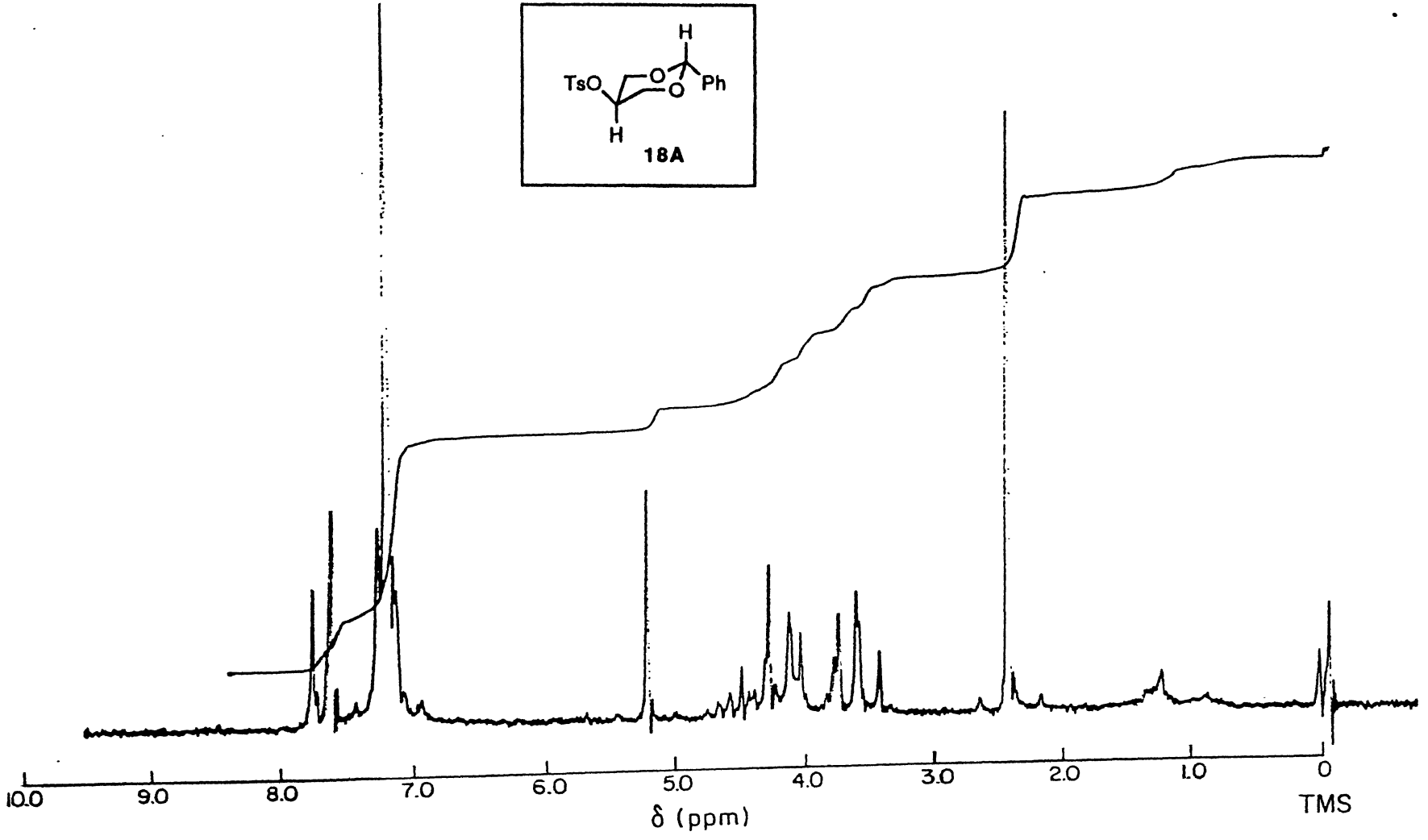


Fig. 2.5 ^{1}H NMR spectrum (60MHz)of 18A

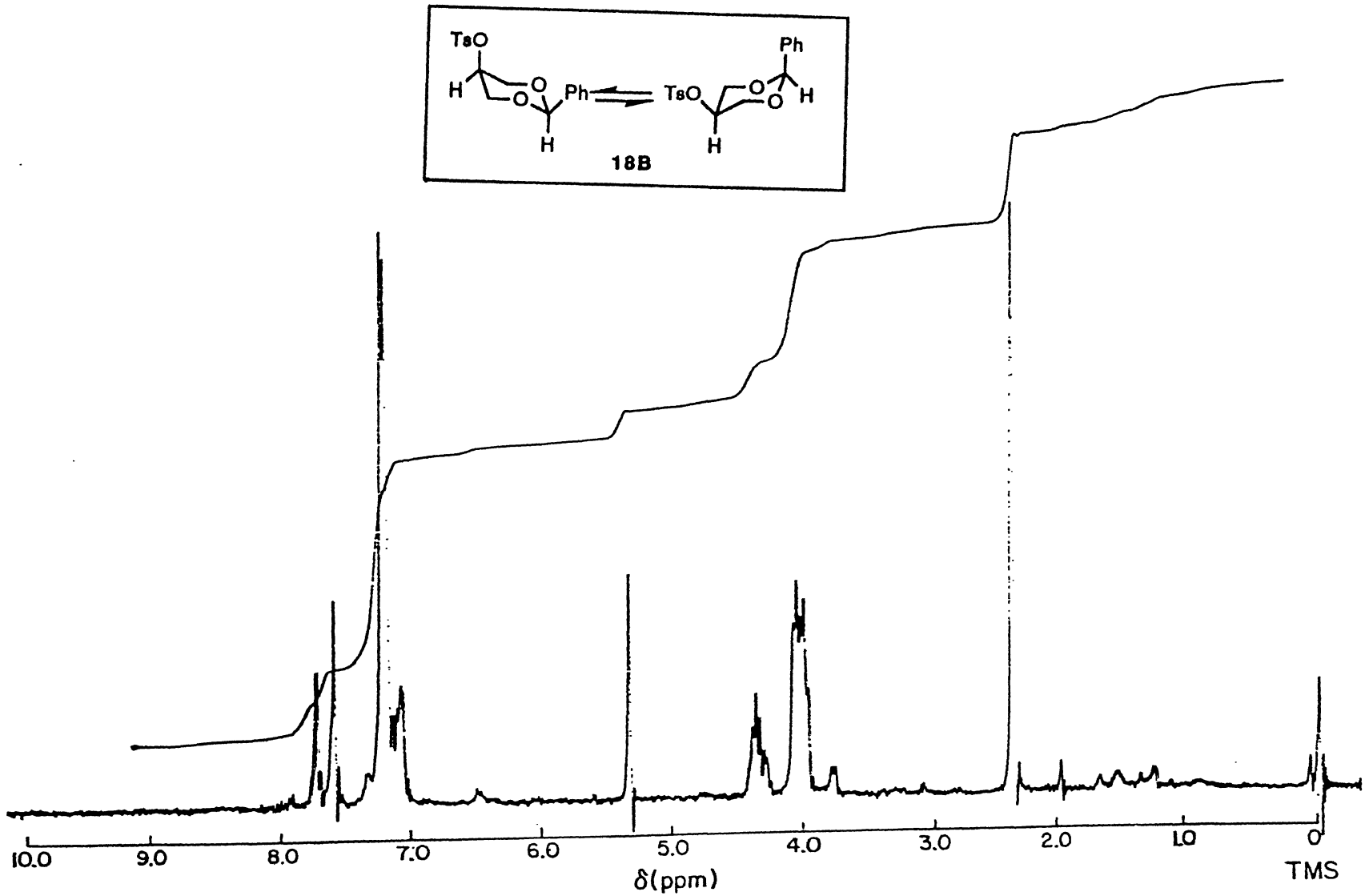


Fig. 2.6 ^{1}H NMR spectrum (60MHz)of **18B**

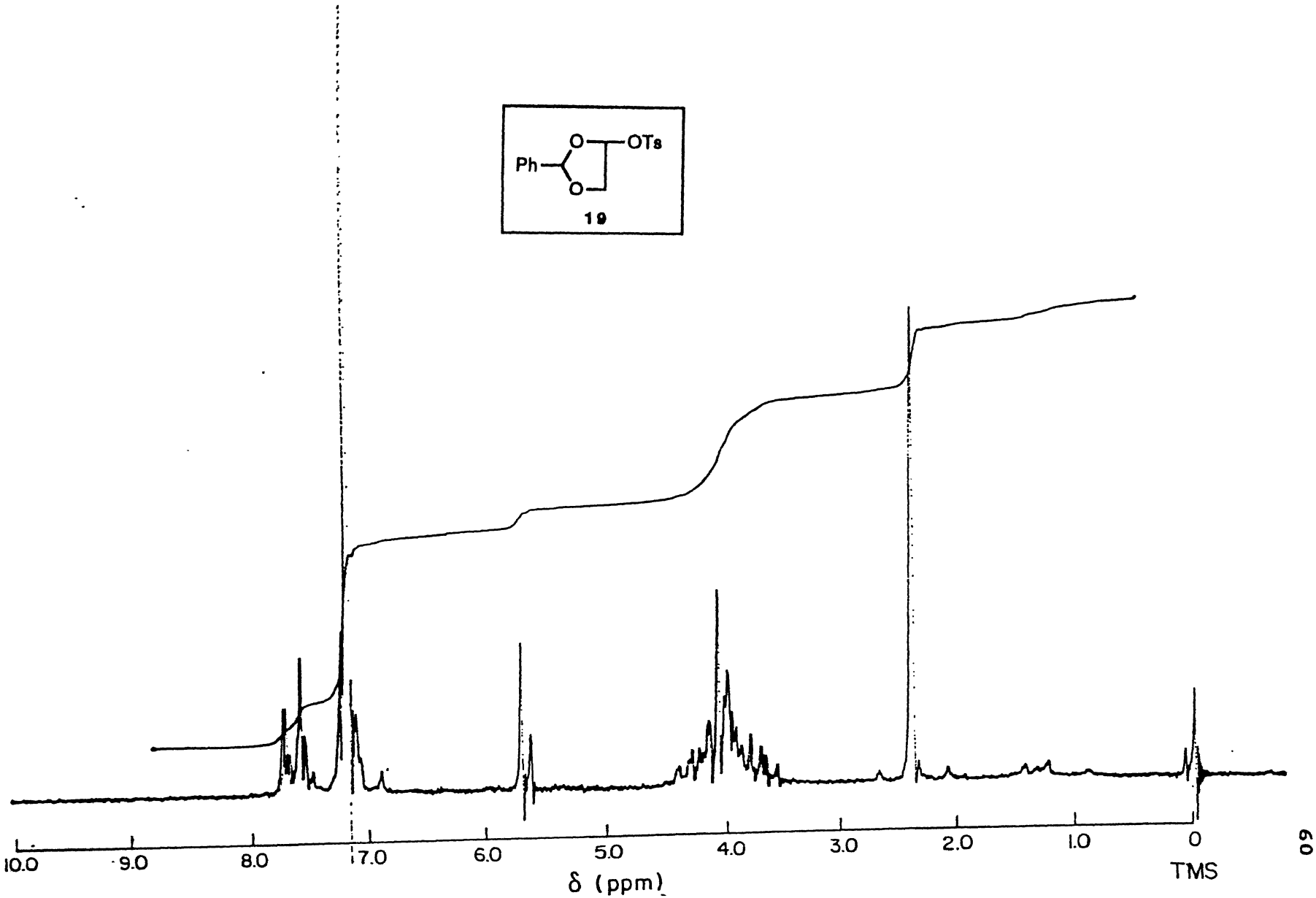


Fig. 2.7 ^{1}H NMR spectrum (60MHz)of **19**

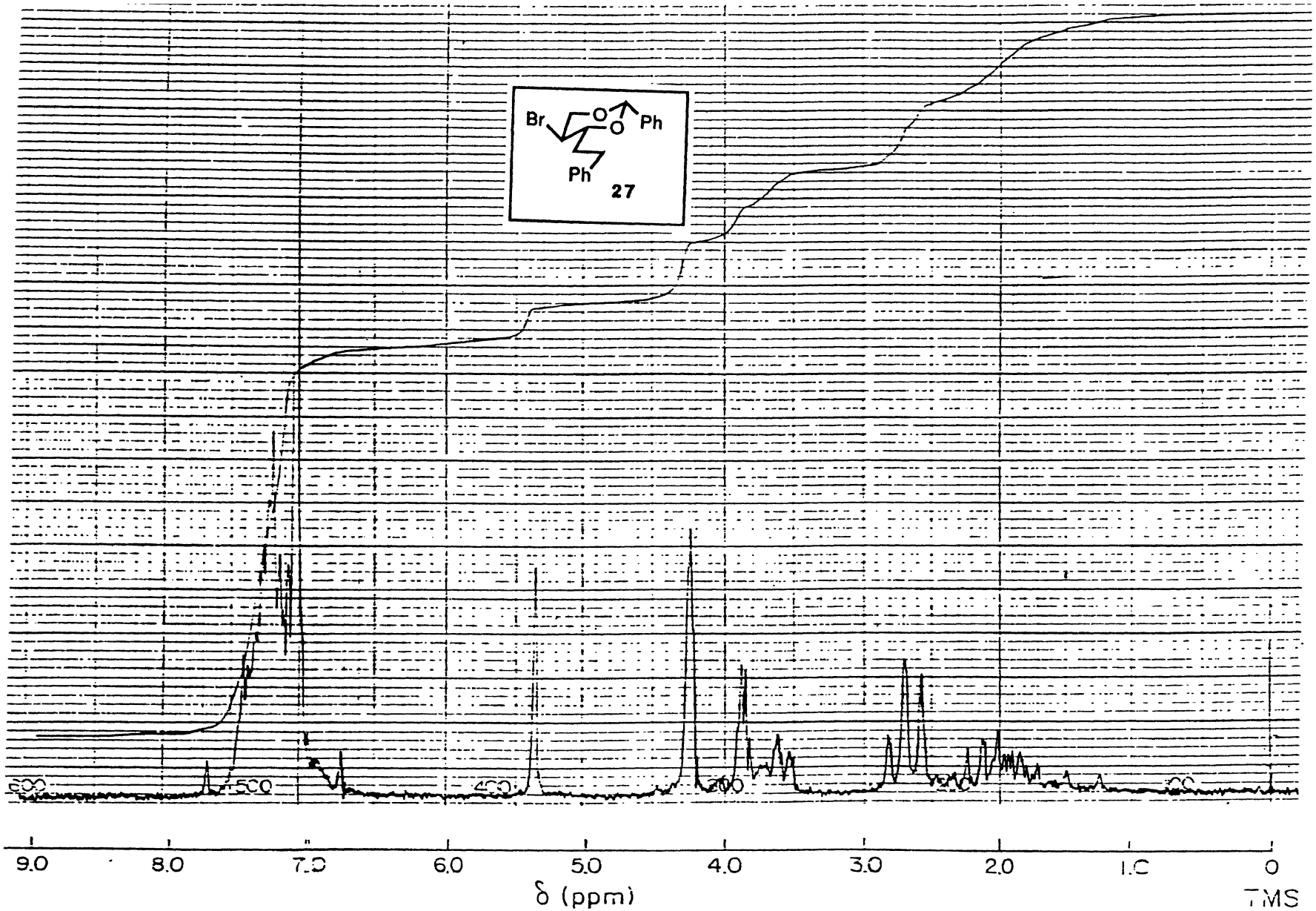


Fig. 2.8 ^{1}H NMR spectrum (60MHz)of **27**

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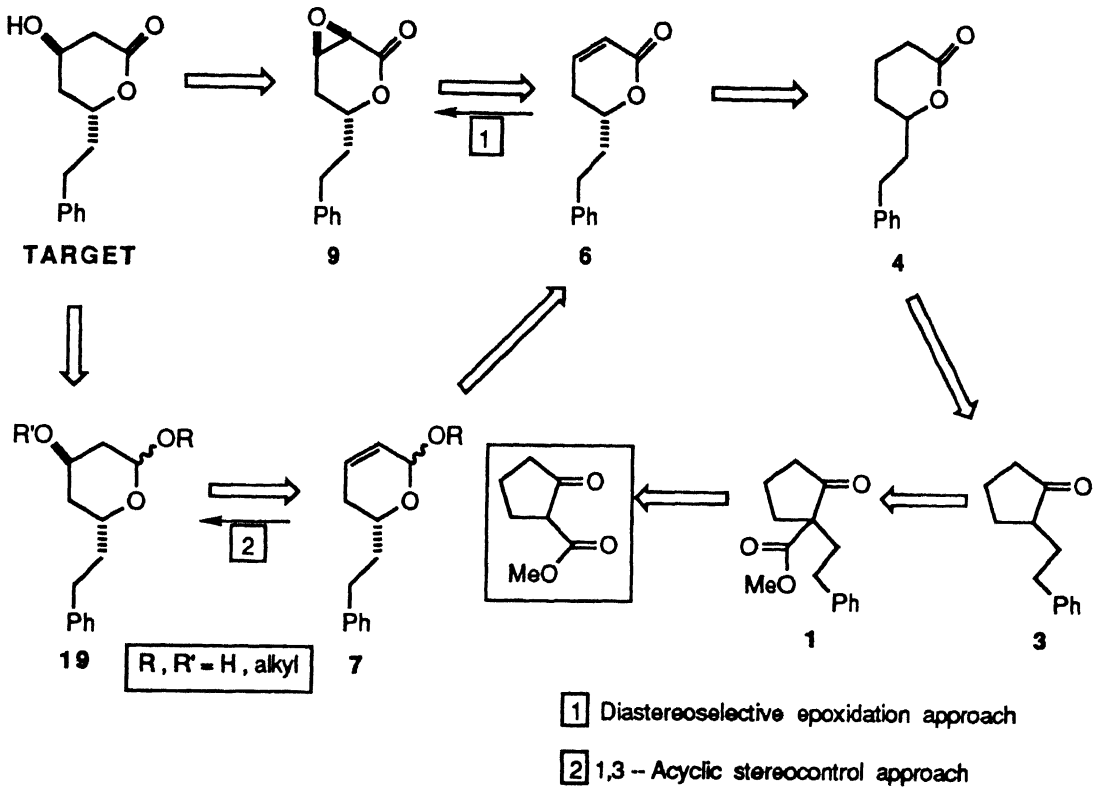
SYNTHESIS OF MEVINIC ACID ANALOGS

(a) Diastereoselective Epoxidation of 3,4-Dehydro-6-(2-phenylethyl)tetrahydropyran-2-one.

(b) Reaction of Methanol with 2-Alkoxy-3,4-dehydro-6-(2-phenylethyl)tetrahydropyran : Revelation of Acyclic 1,3-Diastereoselection

Regioselective scission of C_α-O bond in the α,β-epoxylactone **9** results in the **target molecule** "4-hydroxy-6-(2-phenylethyl)tetra-hydropyran-2-one". The epoxylactone **9** can be obained from either the α,β-unsaturated-δ-lactone **6** by its diastereoselective epoxidation or the enelactol **7**, a reduction product of **6**, by Sharpless-Katsuki asymmetric epoxidation followed by oxidation of

Scheme 3.1.1



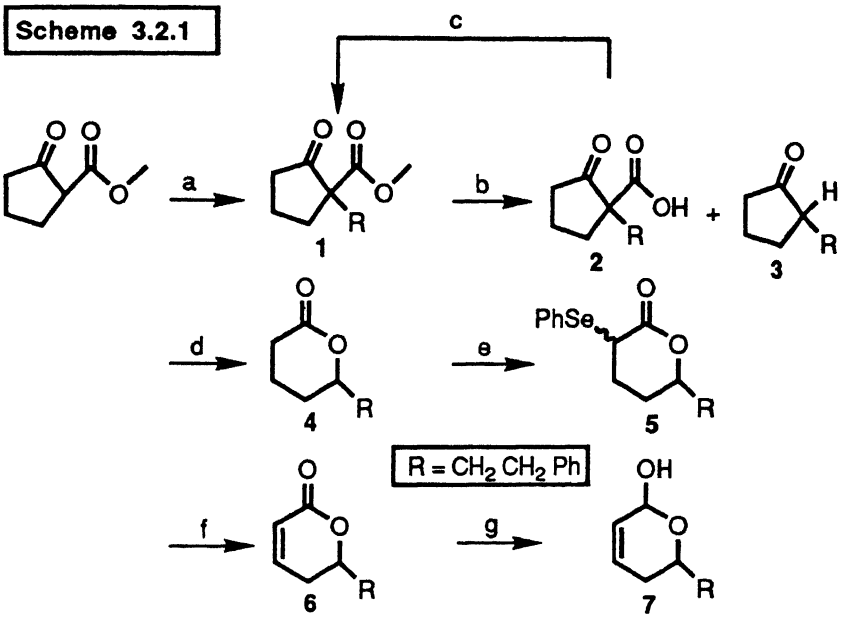
the hemiacetal. Alternatively, the reaction of MeOH with **7** or an ether derived from it in presence of an acid may give the masked lactol **19** which upon sequential acetal-hydrolysis, oxidation, and ether-cleavage shall produce the **target molecule** [Scheme 3.1.1].

The common precursor **6** can be generated from commercially available 2-carbomethoxycyclopentanone using the reaction sequence shown in Scheme 3.2.1.

3.2 Results and Discussion

Alkylation of 2-carbomethoxycyclopentanone with 2-bromoethyl-benzene gave 2-carbomethoxy-2-(2-phenylethyl)cyclopentanone **1**

Scheme 3.2.1



(a) $PhCH_2CH_2Br$, K_2CO_3, NaI (cat), acetone, reflux; 80% (b) LiCl, DMF,145-150 °C; 90% (c) CH_2N_2, Et_2O, 0 °C; quantitative (d) $PhCO_3H$, $CHCl_3$, rt; 95% (e) LDA, THF, - 80 °C, PhSeBr; 95% (f) H_2O_2, pyridine, CH_2Cl_2 ; 94% (g) Dibal-H, toluene, quant

(Scheme 3.2.1). This, when subjected to dealkyldecarboxylation[1] (LiCl/DMF), furnished the desired 2-(2-phenylethyl)cyclopentanone **3** in 70% yield along with 20% of 2-carboxyl-2-(2-phenylethyl)cyclopentan- one **2** (mp 84 - 85 °C). IR [3480-2430, br; 1745-1660 cm^{-1},br]and ^1H NMR [(80 MHz, $CDCl_3$): ppm 10.1 (bs, 1H, COO<u>H</u>), 7.2 (s, 5H, Ar-<u>H</u>), 2.68 (t, 2H, J = 7.5

Hz, $PhC\underline{H}_2$), 2.3 (bs, 2H, $-C\underline{H}_2C(O)$), 2.1-1.2 (m, 6H, $3XC\underline{H}_2$)] are in agreement with the formulation of **2**. Carboxylic acid **2**, on treatment with CH_2N_2, furnished the starting material **1** in almost quantitative yield, hence further confirming the structure **2**.

β-Ketocarboxylic acids are unstable and decarboxylate rapidly on heating. The carboxylic acid **2**, however, refused to submit to decarboxylation under conditions such as (i) heating in toluene with or without $NaHCO_3$, and (ii) heating in xylene with or without $NaHCO_3$. We studied the reaction further and soon discovered that dilution of the reaction solution by DMF led to the decreased amounts of the above acid. The optimum concentration which we arrived at was 1 mmol of ester **1** in 4 ml DMF. Isolation of carboxylic acid in yields stated above was noted when this concentration was doubled, i.e. 1 mmol of **1** in 2 ml DMF. The structure **3** is based on spectral data [disappearance of signal at 3.6 ppm (s, m, $-CO_2C\underline{H}_3$) in ^1H NMR and appearance of a strong band at 1725 cm^{-1} (C=O)], and elemental analysis (cf expt. 3.3.2).

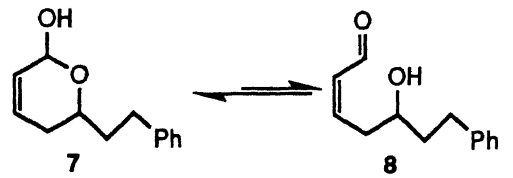
Baeyer-Villiger oxidation of 2-substituted cyclopentanone **3** produced 6-(2-phenylethyl)tetrahydropyran-2-one **4** which was characterized from spectral means (cf expt. 3.3.3). A multiplet at ppm 4.15 in ^1H NMR spectrum and IR absorption at 1730 cm^{-1} are supportive.

Now, the task of introduction of α,β-unsaturation was taken up. The recourse via selenoxide elimination was our choice. Consequently, the lithium enolate of lactone **4** was quenched with benzeneselenenyl bromide[2] to give 2-benzeneselenenyl-6-(2-phenylethyl)tetrahydropyran-2-one **5**. Further, selenoxide formation coupled with its elimination[2] yielded

3,4-dehydro-6-(2-phenylethyl)tetrahydropyran-2-one **6** (IR, ν_{max}: 1720 cm^{-1}). The ^1H NMR spectrum [ppm 7.0 - 6.6 (m, 1H), 5.9 (qd, 1H, J = 12.5 Hz), 4.35 (m, 1H)] of **6** as exhibited in Fig. 3.1 is in agreement with its formulation.

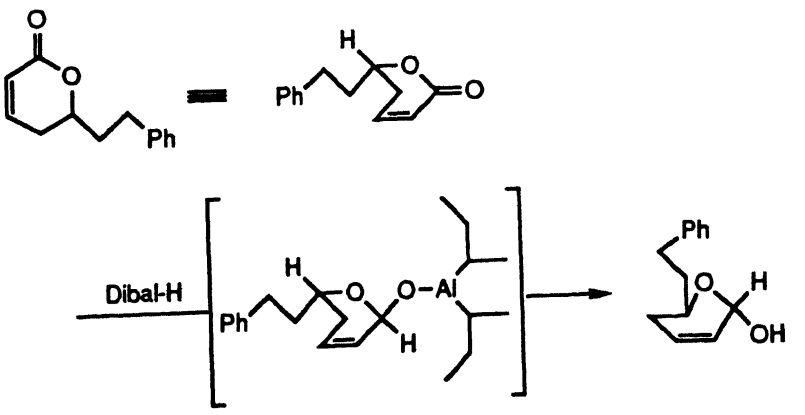
Dibal-H reduction[3] of the carbonyl group of enelactone **6** delivered 3,4-dehydro-2-hydroxy-6-(2-phenylethyl)tetrahydropyran **7**. The IR spectrum shows up strong bands at 3420 (ν_{OH} and 1715 cm^{-1}, the absorption at 1715 cm^{-1} is expected to arise from the

Scheme 3.2.2



aldehyde group of **5**-hydroxy-7-phenyl-2-heptenal **8**, on open chain isomer of the eneleactol **7** (Scheme 3.2.2). The ^1H NMR (Fig. 3.2) and the mass spectrum are in harmony with the formulation of **7**. A signal at ppm 5.41 (s,1H) corresponding to -OC<u>H</u>(OH)- clearly

Scheme 3.2.3



implies that **7** is stereochemically pure. We believe that carbonyl reduction proceeds through a boat like transition state (Scheme 3.2.3). Initial complexation of Dibal-H with the carbonyl oxygen promotes axial hydride delivery to avoid possible steric interference with 2-phenylethyl substituent and benefits from stereoelectronic effects. The product, so produced, is, therefore, a product of steric as well as stereoelectronic control[4]. However, it might very well be that the less stable other isomer is formed first which then isomerizes to the more stable above isomer **7** via the open-chain hydroxy aldehyde **8**.

3.2.1 Diastereoselective epoxidation of 3,4-dehydro-6-(2-phenylethyl)tetrahydropyran-2-one 6

Various reported procedures[#] adopted to carry out the epoxidation of enelactone **6** are depicted below:

(a) Alkaline H_2O_2 in MeOH[3]: Reaction was very slow. Methyl 2,3-epoxy-5-hydroxy-7-phenyl-2-heptanoate **10**, a result of lactone ring opening, was the product isolated in 20% yield along with 54% of starting material. To remedy this problem, MeOH was replaced by non-nucleophilic water miscible solvents such as THF and DME, no reaction was noticed.

(b) t-BuOOH and Triton B in benzene[5a]: Reaction gave a complicated products mixture.

(c) mCPBA in refluxing dichloroethane[5b]: After 6h, about 60% conversion in favor of the desired oxirane was observed (cf. expt. 4.3.2).

 # Details will be discussed in Chapter 4 (Part 4.2) of the thesis.

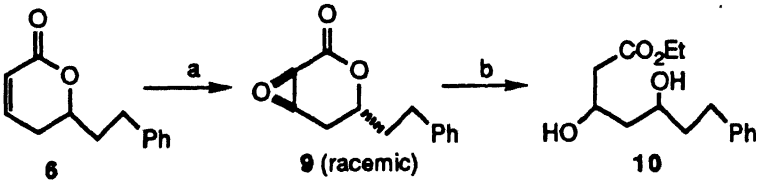
(d) Biphasic reaction in benzene and H_2O with $H_2O_2/NaHCO_3$ in presence of n-Bu_4NI was unyielding

The above unfortunate failures acted as prelude to develop two newer, milder, and easily adaptable reagents[#] for the epoxidation of electrophilic olefins. t-BuOOH in combination with DBU helped us to achieve the requisite oxidation of the unsaturated lactone **6** to deliver 3,4-epoxy-6-(2-phenylethyl)tetrahydropyran-2-one **9** in >75%

The structural identity of **9** is based on its ^1H NMR [Fig. 3.3; disappearance of resonances at ppm 7.0-6.6 (m, 1H) and 5.95 (qd, 1H, J = 12.5 Hz) for the olefinic protons and appearance of resonances at ppm 3.62 (m, 1H) and 3.25 (td, 1H, J = 12 and 3 Hz], IR (1710 cm^{-1}), mass spectrum, and elemental analysis (cf expt. 3.3.7). Presence of only one set of multiplet at ppm 4.53 corresponding to $-CO_2\underline{C}H-$ reveals that compound **9** is probably a single oxirane. Further that this oxirane is the *trans* species is confirmed later from the ^1H NMR spectral features and the optical rotation value of the β-hydroxy-δ-lactone material derived from it.

The known cleavage of α,β-epoxylactone by lithium in liquid NH_3 was not attempted for reasons of reported poor yields[6].

Scheme 3.2.4



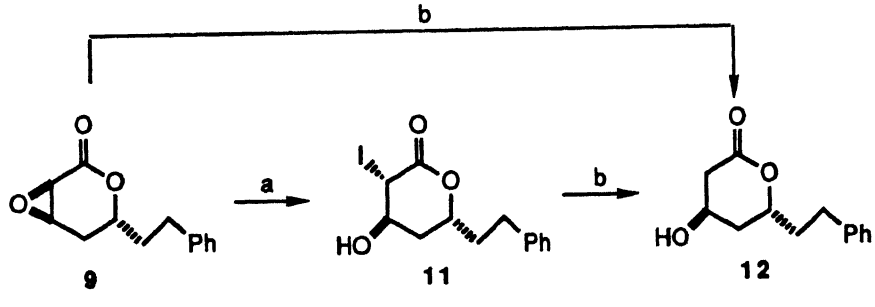
6 **9 (racemic)** **10**

(a) t-BuOOH, DBU, dichoroethane, rt; 75%
(b) $NaBH_4$, PhSeSePh, AcOH, EtOH; 20%

Reaction with sodium phenylselenotriethoxyborate ($NaBH_4$/PhSeSePh /EtOH)[7] gave a compound which was not the desired 4-hydroxy-6-(2-phenylethyl)tetrahydropyran-2-one. This assignment was made on the basis of IR (3420 and 1710 cm^{-1}) and ^1H NMR [ppm 7.3 (s, 5H), 4.5-3.8 (m, 4H), 3.8-3.0 (m, 2H), 3.0-2.6 (m, 2H), 2.5 (d, 2H, J = 7 Hz), 2.05-1.5 (m, 4H), 1.3 (t, 3H, J = 7.5 Hz] spectra. Further, these spectral data conform to the formation of ethyl ester **10** of 3,5-dihydroxy-7-phenyl heptanoic acid (Scheme 3.2.4), a product derived from the opening of the expected hydroxy lactone formed during the reaction. Further confirmation to the formulation of **10** comes from its mass spectrum [m/z: 266 (M^+)] and elemental analysis [calcd.for $C_{15}H_{22}O_4$: C, 67.67, H, 8.27; Found: C, 67.30, H, 8.10%].

Rennecke et al have reported[8] the α-cleavage in α,β-epoxy ketones using NaI in acetone under buffered conditions. When this reagent system (NaI/NaOAc, AcOH, Acetone, rt) was applied to the epoxylactone **9**, the expected intermediate 4-hydroxy-3-iodo-6-(2-phenylethyl)tetrahydropyran-2-one **11** was isolated in 50% yield;

Scheme 3.2.5



(a) NaI, AcONa, AcOH, acetone; 50% coversion (b) NaI, 2-butanone, reflux; 70%

the rest being the starting material and a little of the desired β-hydroxy-δ-lactone **12** (Scheme 3.2.5). The structure assigned to **11** is based on IR (ν_{max} : 3415 and 1720 cm^{-1}) and ^1H NMR [7.3 (s, 5H), 4.75-4.05 (m, 2H, -COOC<u>H</u>-, C<u>H</u>OH), 4.5-3.8 (m, 1H, C<u>H</u>I), 3.0-2.65 (m,2H, PhC<u>H</u>$_2$), 2.5-2.15 (m, 2H, ring methylene-<u>H</u>), 2.1-1.7 (m, 3H, methylene-<u>H</u>, O<u>H</u>)] spectra. Mass spectrum [m/z: 347 (M^+) further supports the formulation of iodohydrin **11**.

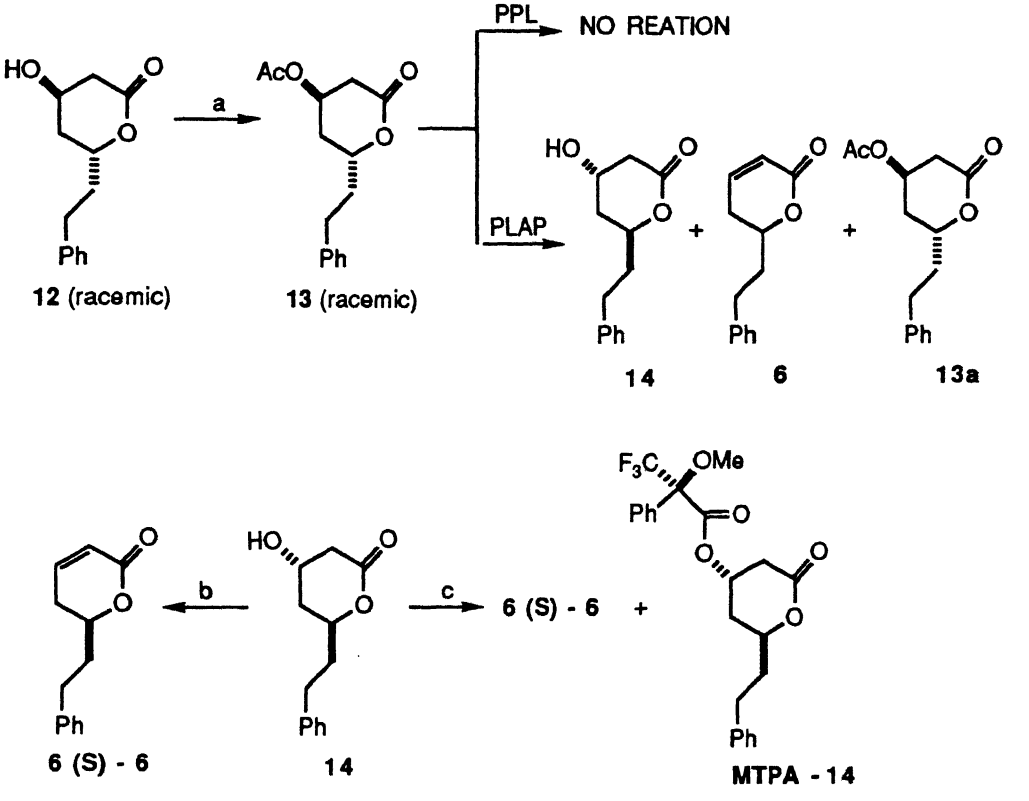
The iodohydrin **11** was unstable because it reverted slowly to the starting epoxide **9** at rt, and also when passed through a short silica gel column. When refluxed with 5 equivalent of NaI in 2-butanone for 3 hours, it gave the expected β-hydroxy-δ-lactone **12** (70%; 35% from **9**). Interestingly, under similar conditions the epoxy lactone **9** furnished the desired compound **12** in 85% yield. The formulation of **12** derives from its IR (3420 cm^{-1}), other spectral data and elemental analysis (cf expt. 3.3.8). ^1H NMR of **12** is depicted in Figure 3.4.

Obviously, **12** is a mixture of diastereoisomeric alcohols. In order to effect the resolution of these alcohols by biocatalysts, alcohols were converted into the corresponding acetates **13** with Ac_2O and pyridine in presence of 4-dimethylaminopyridine (DMAP). The formation of acetates is established by spectral means (cf expt. 3.3.9). ^1H NMR spectrum of **13** is exhibited in Fig. 3.5.

To accomplish the resolution, recemic acetate **13** was subjected to procine pancreatic lipase (PPL, type VI-S, EC 3.1.1.3, sigma) hydrolysis[9]. After 8 days, no hydrolysis was noticed and only the starting material **13** was isolated intact. This observation is in agreement with the known specificity of PPL for esters of primary alcohols[10].

The next biocatalyst we examined was the freshly prepared pig liver acetone powder (PLAP)[11]. The result was promising. The alcohol **14** (Scheme 3.2.6) was isolated, after chromatography, in 86% yield; based on the assumption that only half of the acetate would react under conditions of complete disasteroselection.

Scheme 3.2.6



(a) Ac_2O, pyridine, CH_2Cl_2 ; 76% (b) R-(+)-MTPA-Cl, Et_3N, DMAP, CH_2Cl_2, 0 °C– rt, 6h; quantitative (c) R-(+)-MTPA-Cl, pyridine, DMAP, CH_2Cl_2, 0 °C, 6h

Surprisingly, the unreacted acetate was not isolated in pure form. Instead, it contained ~60% of enelactone **6**. The unsaturated lactone **6** appears to have arisen from dehydrodeacetoxylation of 4(R),6(R)-**13**. This, however, we have not confirmed.

The compound **14** exhibits optical rotation $[\alpha]_D^{25} = -42.5^o$, c = 10 mg/2 ml $CHCl_3$; lit[12] $[\alpha]_D^{25} = -45.2^o$, c = 0.44, $CHCl_3$. The absolute stereochemistry of **14**, therefoe, is 4S,6S, and, hence,

this is the unnatural diastereoisomer. Calculations based on optical rotation data, both ours and that literature, project **14** to have 94% ee. To further ascertain the optical purity of 4S-6S-**14**, we ventured to prepare Mosher's ester **MTPA-14** (Scheme 3.2.6). Compound **14**, on reaction with R-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetyl chloride [(R)-(+)-MTPA-Cl] and triethyl amine in presence of dimethylaminopyridine (DMAP) in catalytic amount[12], gave enelactone 6(S)-**6**. Replacing triethylamine by pyridine afforded an inseparable mixture of the requisite **MTPA-14** and 6(S)-**6** in ~60:40 ratio (^{1}H NMR; Fig.3.6). Comparing the ^{1}H NMR spectrum of **MTPA-14** with that of Mosher ester of recemic alcohol **12** (Fig. 3.6B) it was unmystified that methoxy protons at ppm 3.50 and 3.41 correspond to different diastereoisomers. Using their integration ratio as a handle, the optical purity of **MTPA-14** was calculated to be >90%.

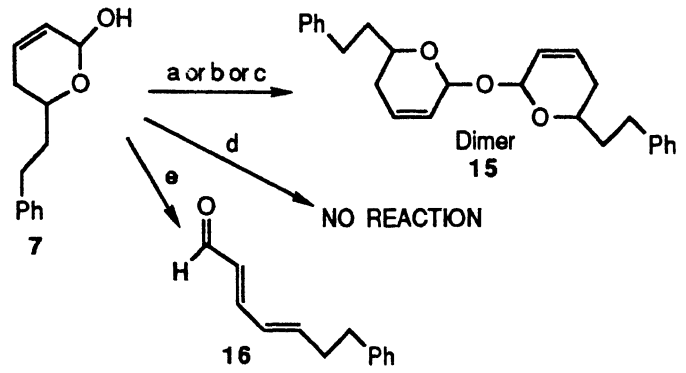
The above mentioned transformations constitute an enzyme-catalysed optically active synthesis of an unnatural mevinolin analog.

3.2.2 Reaction of MeOH with 2-alkoxy-3,4-dehydro-6-(2-phenylethyl) -tetrahydropyran : Revelation of acyclic 1,3-diastereoselection

While we were exploring to oxidise the α,β-unsaturated-δ-lactone **6** to obtain α,β-epoxylactone **9**, we contemplated to oxidise the enelactol **7** under Sharpless asymmetric epoxidation conditions[13]. This reaction, however, failed and, instead, the dimer **15** (Scheme 3.2.7) was isolated. The structure

assignment of **15** is due to mainly to the disappearance of IR band at 3420 cm^{-1} due to the hydroxyl group in **7** and the mass

Scheme 3.2.7



(a) t-BuOOH, $VO(acac)_2$, toluene, 0 °C (5h), 90 °C (0.5h)
(b) t-BuOOH, $VO(acac)_2$, PhH, reflux, 4h
(c) Silica gel column chromatography
(d) PhH or $PhCH_3$, reflux, 4h (e) PhH, p-TSA (cat), reflux, 1h

measurement data m/z = 390 (M^+). ^1H NMR spectrum and elemental analysis (cf. expt. 3.3.14) are also in tune with this structure assignment.

On one occasion, we passed the lactol **7** through a silica gel column to remove some minor unidentified impurity. The result was a surprising isolation of **15**. The formation of dimer **15** may be conceived due to

(a) protonation of enelactol,

(b) elimination to H_2O to give allyloxonium ion **17**, and

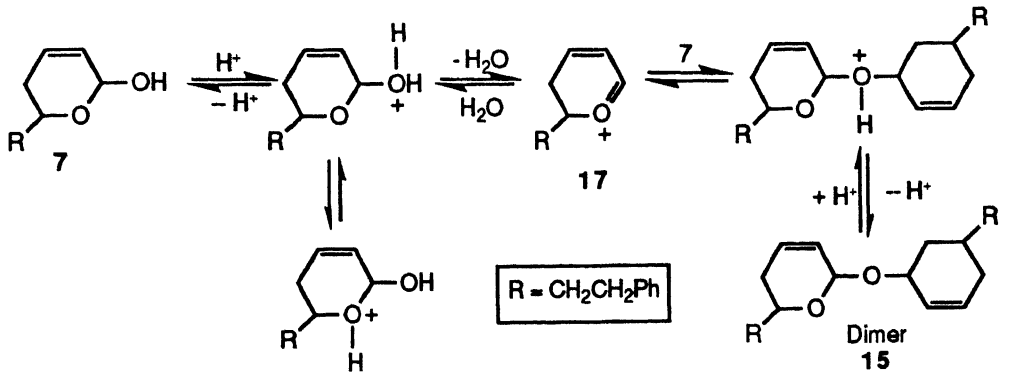
(c) capture of **17** by another molecule of the enelactol in Ferrier 1,2-fashion[18] (Scheme 3.2.8).

Such a dimerization failed on subsequent occasions.

We next attempted to find reaction conditions that would give

consistent results on the above dimerization front. The enelactol **7** is stable in refluxing benzene and toluene. The relux of **7** in

Scheme 3.2.8



benzene in presence of p-TSA (10 mol% wrt **7**) furnished 7-phenylhept-2,4-dienaldehyde **16** as the sole product. The evidence to the structural identity of **16** comes from the following spectral data and elemental analysis:

IR (neat), ν_{max} : 2820 and 2730 (aldehyde C-H), 1690 cm^{-1} (conjugated aldehyde)

^{1}H NMR (80 MHz) : ppm 9.56 (d, 1H,J = 7.5 Hz), 7.48- 6.8 (m, 7H, -C<u>H</u>=CH-C<u>H</u>=CH-CHO and Ar-<u>H</u>), 6.42-5.84 (m, 2H, -CH=C<u>H</u>-CH=C<u>H</u>=CHO), 3.0-2.37 (m, 4H, PhC<u>H</u>$_2$C<u>H</u>$_2$).

U.V. $\lambda_{max}^{CHCl_3}$: 275 nm.

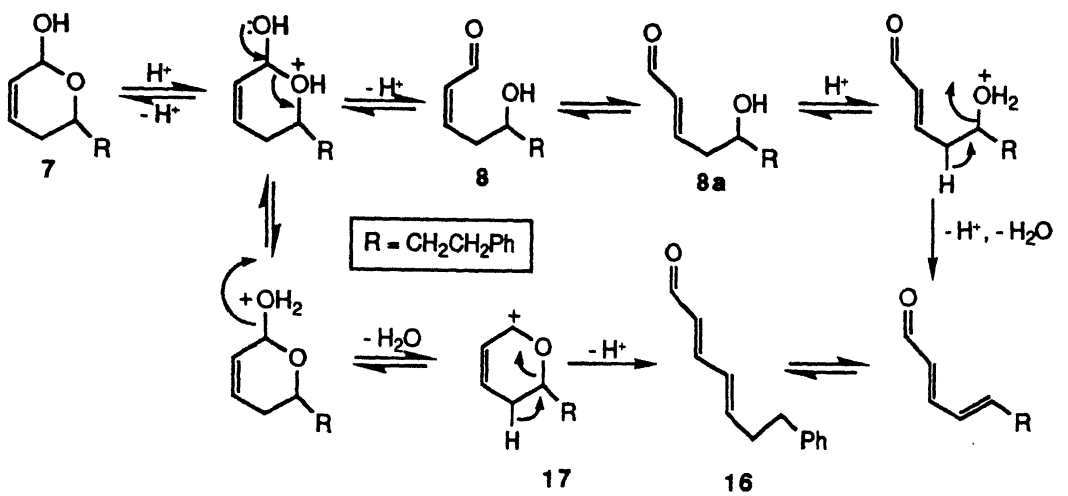
Mass (m/z) : 187 (M^++1), 186 (M^+).

Analysis calcd.for $C_{13}H_{14}O$: C, 83.87, H, 7.52;
Found : C, 83.60, H, 7.37%.

As shown in Scheme 3.2.9, protonation of enelactol, ring opening followed by *cis-trans* isomerization gives the intermediate

8a which undergoes H^+ assisted elimination of H_2O to furnish the dienaldehyde **16**. The necessary driving force for elimination comes from the enhancement in conjugation to aldehyde. Alternatively, the formation of **16** can also be rationalised

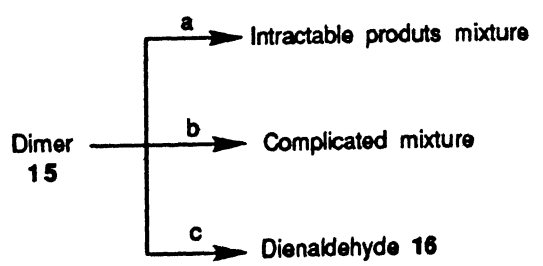
Scheme 3.2.9



through the allylic carbonium ion **17** and electron movement as shown.

The reaction of the dimer **15** with mCPBA in dichloroethane resulted in a complicated mixture. Reflux with p-TSA (10 mol%

Scheme 3.2.10

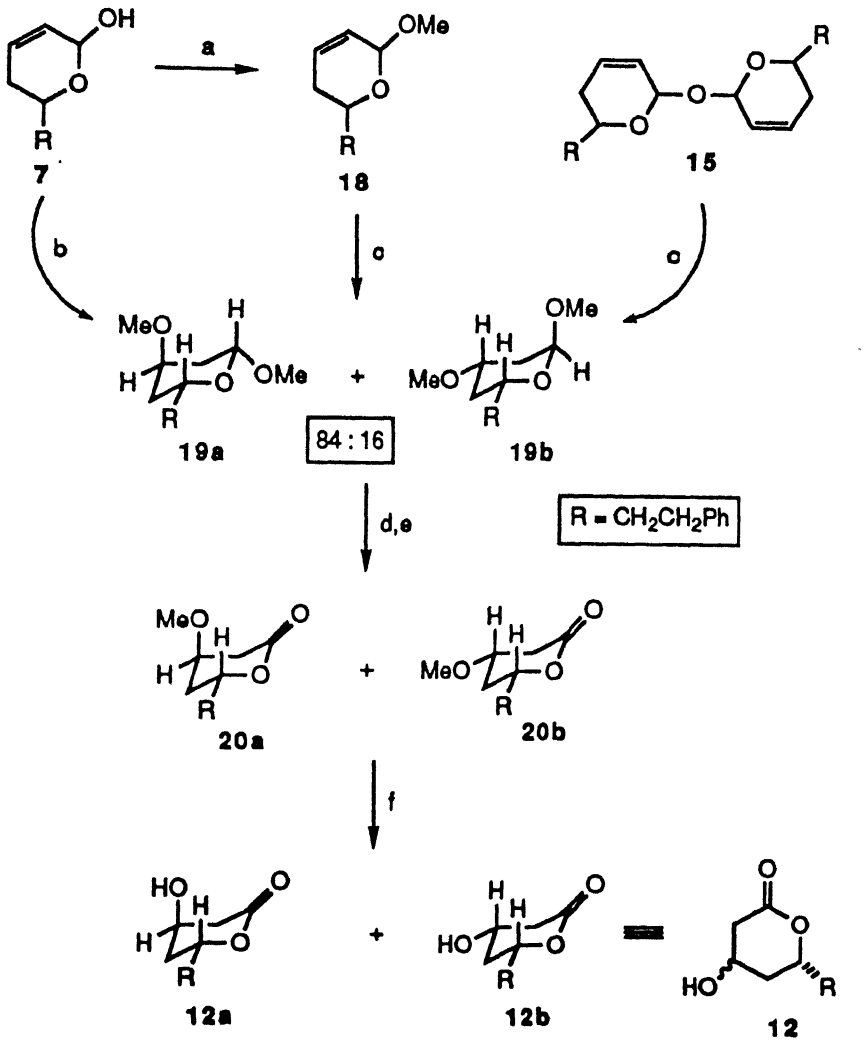


(a) mCPBA, CH_2Cl_2 (b) p-TSA, PhH, reflux, 1h
(c) Dioxane: H_2O : 5% aq HCl = 10 : 1 : 1), rt, 4h

wrt **15**) in dry benzene furnished, once again, a complicated mixture. Treatment with aqueous acid in dioxan (Scheme 3.2.10) furnished only the dienaldehyde **16**.

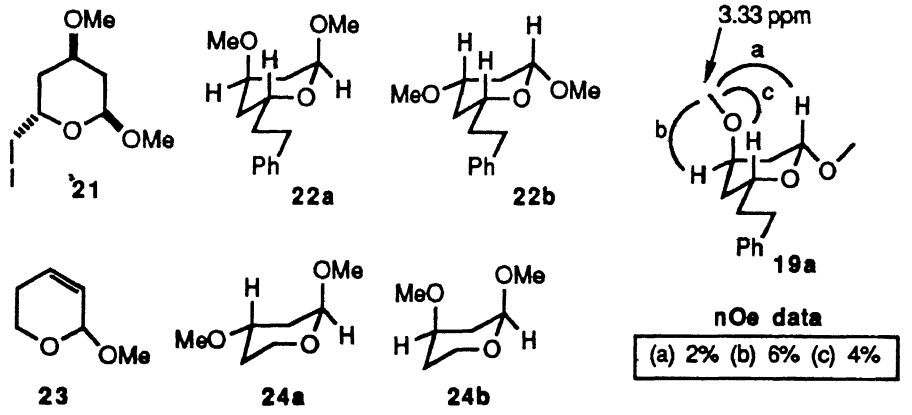
The enelactol **7** was tranformed[14] into the acetal **18** (cf expt. 3.3.13). The acetal **18** was refluxed in MeOH with a

Scheme 3.2.11



(a) $BF_3 \cdot OEt_2$, MeOH, Et_2O, 0 to 20 °C; 80% (b) MeOH, conc HCl (cat), reflux, 3h; >95% (c) MeOH, conc HCl (cat), reflux, 6h; 95% (d) 10% aq HCl : THF = 3 : 5, 45 °C, 1h (e) Fetizon's oxidn; 86% for steps d & e (f) BBr_3, CH_2Cl_2; 45%

catalytic amount of concentrated HCl. This furnished 2,4-dimethoxy-6-(2-phenylethyl)tetrahydropyrans *arabino* **19a** and *xylo* **19b** (Scheme 3.2.11). ^{1}H NMR spectrum of the mixture **19** is given in Figure 3.7. Resonances at 4.87 (bs) and 4.6 (dd, J = 10 and 2.5 Hz) have been ascribed to the equatorial and axial acetal protons present in compounds **19b** and **19a** respectively. These assignments are based on the values of coupling constants. The structural identity of compounds **19a** and **19b** has further been corroborated from the ^{1}H NMR spectrum of 6-iodomethyl-2,4-dimethoxytetrahydropyran **21**[15]. Other spectral data (cf expt 3.2.15) are in line with the formation of **19**. Compounds **19a** and **19b** are formed, interestingly, in a ratio 84:16 (^{1}H NMR). Correlation spectroscopy (COSY) (Fig. 3.8), and nOe experiments further support the formulation of **19**. Saturation of



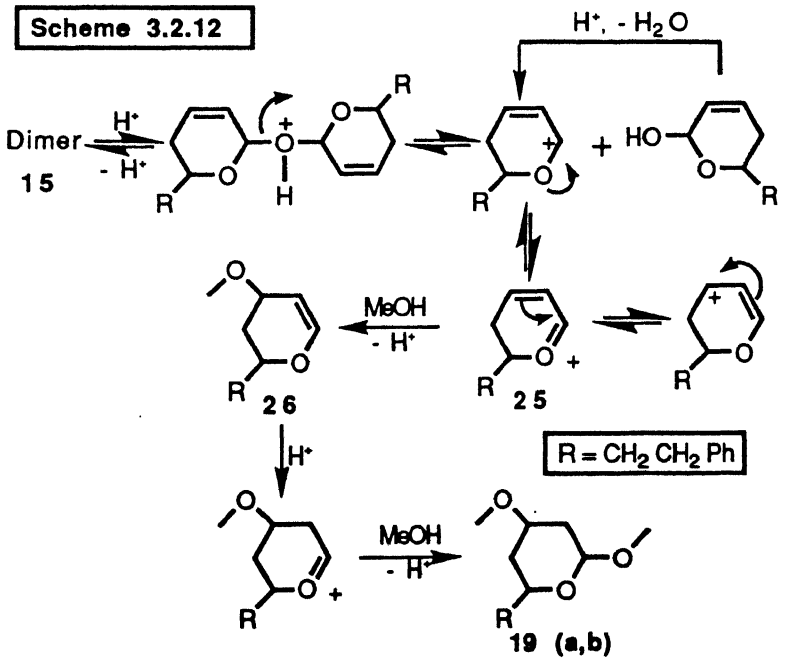
4-OMe signal (ppm 3.33) in the major isomer **19a** exhibited 4% nOe enhancement for the C-6 proton; revealing their *cis*-relationship and, hence, the axial nature of both.

The preponderance of *arabino* structure **19a** over the *xylo* **19b** is in contradiction to the earlier findings of Zamojski et al[16].

The higher proportion of **19a** is indicative of enhanced kinetic control during the reaction. The related *ribo* **22a** and the *lyxo* **22b** structures were absent. While working with 6-carbomethoxy derivative, Zamojski et al received, unlike us, only a 1:1 distribution of the *arabino* and *xylo* species from a reaction in methanol containing 1% HCl (kinetic conditions). In work with 6-unsubstituted 2-methoxy-5,6-dihydro-2H-pyran **23**, Sweet and Brown[17] isolated 2,4-dimethoxytetrahydropyrans **24a** and **24b** constituted in 4:1 proportion. Anomeric effect was the guiding factor. Obviously, the anomeric effect is less important in **19a** for reasons of more stringent 1,3-diaxial interactions.

A priori, the high stereoselectivity may be conceived due

Scheme 3.2.12



probably to a three stage process (scheme 3.2.12); namely,

(a) dimer **15** breaks down to the cyclic allyl carbonium ion **25**.

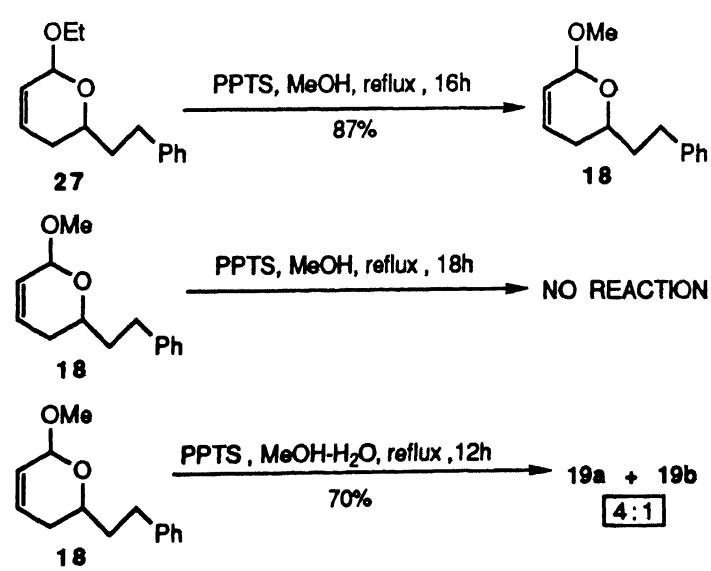
(b) unlike normal Ferrier reaction[18], MeOH enters through 1,4-addition and largely under the steric guidance of 2-phenylethyl group. The 2-phenylethyl group, being conformably disposed equatorially, directs the incoming MeOH to C-4 *trans* to it, i.e. MeOH enters largely axial in **25** to furnish the enol ether **26**, which

(c) reacts normally, but now under the more prominent steric influence of the axial methoxy group introduced in step (b) above, with MeOH to generate the observed products **19**.

Carbonium ion **25** is recognised as the key intermediate in the Ferrier reaction. A mechanism similar to the above has been earlier proposed by a Polish group[16].

To reflect upon the integrity of the above mechanism, we designed the following experiment (Scheme 3.2.13):

Scheme 3.2.13



2-Ethoxy-6-(2-phenylethyl)-3,4-dehydrotetrahydropyran **27**, obtained from the enclatol **7** by following a procedure similar to that for the preparation of **18**, gave, on reflux in carefully dried MeOH in the presence of cataltic amounts of thoroughly dried pyridinium p-toluene sulfonate (PPTS), the methyl ether **18** in 87% yield. No formation of bismethoxy material **19** was observed.

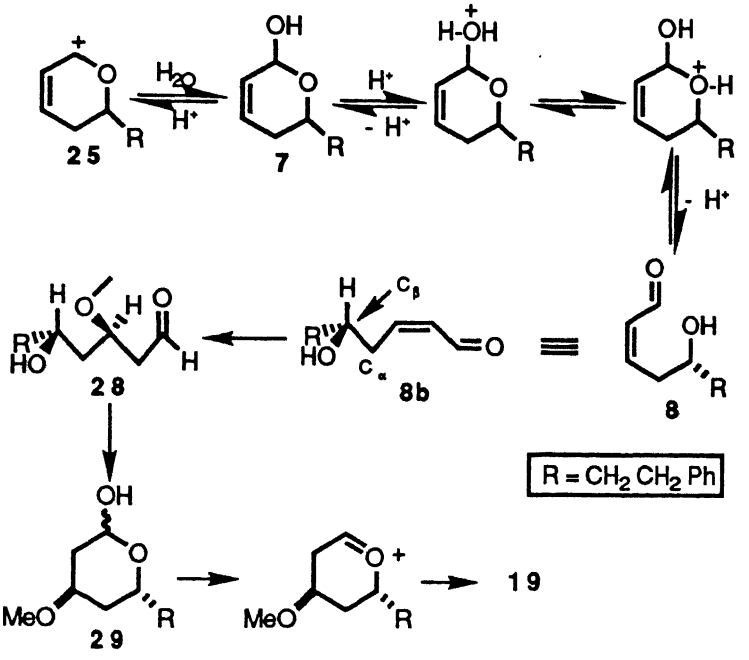
This observation negates the above proposed mechanistic rationale because, had it been operative, the bismethoxy compound **19** should have been produced through the intermediate allyloxonium ion **25**. Obviously, the carbonium ion **25** is formed and is captured by MeOH in Ferrier 1,2-fashion[18] and not 1,4- as proposed earlier by the Polish group[16], the Canadian group[17] and ourselves.

We believe that the H_2O present under the conditions of conc. HCl treatment plays significant role on the course of the reaction. In partial confirmation of the possible role of H_2O, methyl ether **18** was found unreacting on reflux in anhydrous MeOH and carefully dried PPTS (Scheme 3.2.13). However, deliberate inclusion of few drops of H_2O resulted in noticeable change in favor of the bismethoxy derivative **19** (Scheme 3.2.13). This transformation was, however, relatively slower than that observed with conc. HCl. The yield of bismethoxy product **19**, after isolation and chromatographic purification, was 70% (*arabino* and *xylo* species in the ratio of ~4:1; ^1H NMR).

We postulate that the role of H_2O is possibly to intervene at the allyl oxonium ion stage **25**, transforming it into the enelactol **7**. This, in a subsequent step, opens up[19-21] to δ-hydroxy-α,β-unsaturated aldehyde **8**. This adopts the

conformation **8b** (Scheme 3.2.14) in which the smallest substituent H at the stereogenic centre is in the plane of the conjugated system and the σ-plane of conjugate system bisects the angle

Scheme 3.2.14



between the medium **OH** and the largest **R** groups. Such a transition state conformation has been earlier proposed by Fleming et al[22]. 1,4-Addition of MeOH from the face *anti* to the bulkier group **R** furnishes **28**. The relative stereochemistry in **28** is that present in the product **19a** formed in dominance.

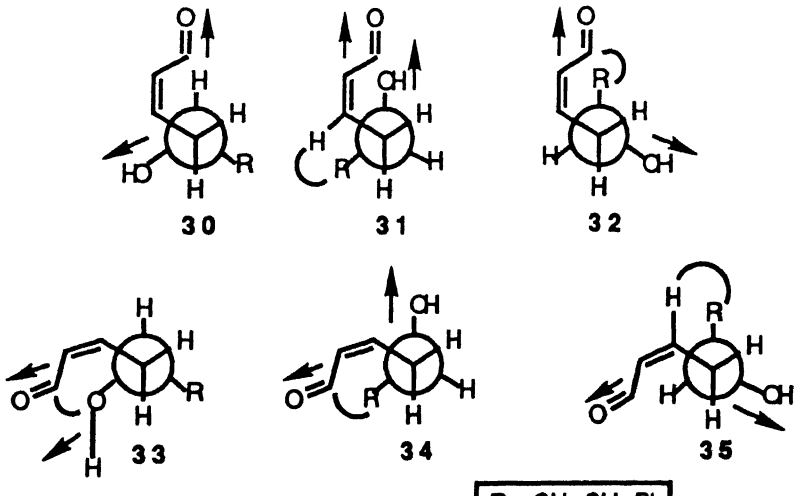
Alternatively, we believe that in MeOH as reaction medium, the **OH** function may get solvated and deliver hydrogen bond-assisted MeOH for conjugate attack on the olefin face *syn* to it. This may, in principle, be considered close to an intramolecular process.

The aldehyde **28** undergoes, through least motion rotation, intramolecular hemiacetalization followed by cyclic onium ion formation and quench by MeOH, in that order, to furnish the eventual major product.

The configuration at the anomeric centre (equatorial in the major and axial in the minor isomer) is dictated exclusively by the methoxy group at positon 4 : (a) axial 4-OMe directs MeOH enter equatorial to avoid 1,3-diaxial interactions, and (b) the equatorial 4-OMe directs MeOH enter axial for both steric as well as electronic reasons. That the hydrogen on anomeric carbon is indeed axial in the major isomer and equatorial in the minor one has been discerned from their coupling patterns[15] as discussed before.

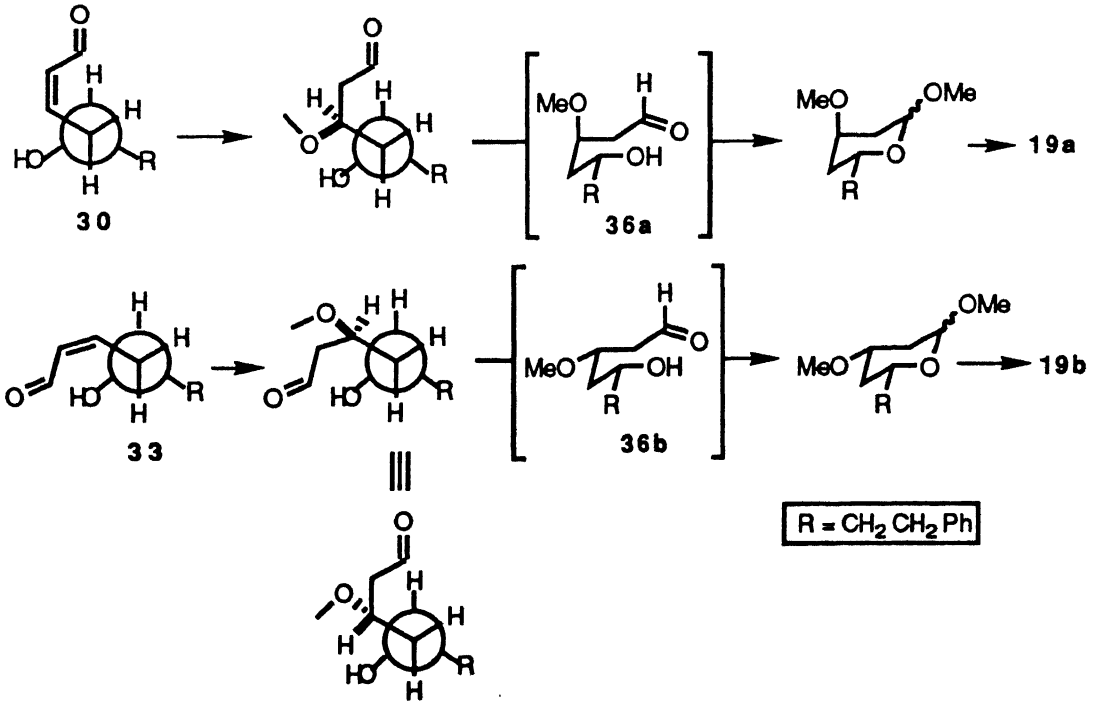
Other transition state models that could be constructed are **30-35** (Scheme 3.2.15), each benefitting from having the β-carbon (the stereogenic centre) oriented perpendicular to the σ-plane of

Scheme 3.2.15



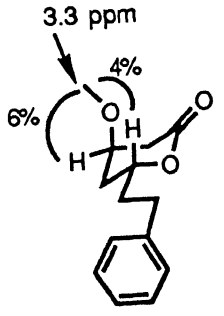
the *ene* function. This is in accord to the Felkin's earlier observation[23] that the staggered conformation between C_α and the trigonal carbon undergoing reaction is preferred. Conformation **30** is derived from least motion rotation away from the larger 2-phenylethyl substituent and benefits from minimization of both the dipole interactions and the non-bonded interactions. In contrast to this, the conformation **33**, which is derived from further rotation around the C_α-C_{sp^2} σ-bond, suffers from both the above interactions. Other conformations suffer from one or the other type of interaction indicated (non-bonded interactions by bent bond and dipole interactions by arrows). 1,4-Addtion of MeOH proceeds from the direction away from C_β in conformation **30** to make available the major isomer **19a** while that in conformation **33**

Scheme 3.2.16



furnishes the minor isomer **19b** as shown in Scheme 3.2.16. This model, however, does not benefit from the "kind of intramolecular" MeOH delivery which the model **8b** (Scheme 3.2.14) may be conceived to enjoy. A model similar to **30** has recently been proposed by Evans[24].

The acetals **19** were subjected to acetal hydrolysis and Fetizon-oxidation and transformed into lactones **20** in a combined 86% yield. Structure determinations are based on ^{1}H NMR (Fig.3.9), IR,Mass, correlation spectroscopy (COSY) (Fig.3.10), and elemental analysis (cf expt 3.3.17). In the ^{1}H NMR spectrum of **20**, there are resonances at ppm 4.55 (m) and 4.14 (m) apart from other characteristic signals. These multiplets have arisen due to protons at position **6** in **20**. The proton on C-6 in **20a** being *syn* to C-4 OMe resonates downfield as compared to that in **20b**. Further evidence corroborating the *syn* relationship of C-4 OMe and C-6 H in the major diastereoisomer **20a** comes from nOe data



20a

nOe data

as shown below. The materials **20a** and **20b** are found to exist in 84:16 ratio (^{1}H NMR). Unmasking of C-4 OH group was achieved by treatment of **20** with BBr_3 in dichloromethane in 45% isolated yield (Scheme 3.2.11). The product alcohol displayed spectroscopic

characteristics identical to that of **12**.

The transformations above, therefore, constitute a formal total racemic synthesis of a mevinic acid analog in which the octalin segment is replaced by 2-phenylethyl substituent.

3.3 Experimental

General: All chromatographic separations were performed over silica gel (100-200 mesh) using petroleum ether (60-80) and ethyl acetate mixtures as eluant. Ether, wherever used, stands for diethyl ether. The organic extracts were dried over anhdyrous Na_2SO_4. Commonly used abbreviations are used throughout. Solvents used in this study were dried as per established procedures. Product(s) solutions were freed of solvent under reduced pressure on rotovap. IR and mass spectra were recorded, respectively, on Perkin-Elmer 1320 and Jeol D-300 series of instruments. ^1H NMR spectra were recorded on either Bruker WM-400 ($CDCl_3$) or Bruker-300 ($CDCl_3$) or Bruker WP-80 ($CDCl_3$) or Jeol PMX 60 MHz (CCl_4) series of spectrometer with TMS as an internal standard (chemical shifts in ppm, and coupling constants in Hz). COSY, NOESY and decoupling experiments were recorded at 400 MHz on a Bruker WM spectrometer.

Perbenzoic acid[25], diphenyldiselenide[26] and 48% Ag_2CO_3 on celite[27] were prepared using known procedures.

3.3.1 2-Carbomethoxy-2-(2-phenylethyl)cyclopentanone 1

A suspension of anhydrous K_2CO_3 (13.8 g, 100 mmol) in a solution of 2-carbomethoxycyclopentanone (7.1 g, 50 mmol), 2-phenylethylbromide (12.0 g, 65 mmol) and NaI (0.15 g, 1 mmol) in

dry acetone (250 ml) was refluxed for 48 h. The reaction mixture was cooled to rt and filtered. The solid was washed with acetone (3 x 25 ml). The residue obtained after removal of acetone was taken in ether (150 ml) and washed with H_2O (2 x 40 ml) and brine (1 x 40 ml). The ether solution was dried and filtered off. The solvent was removed and the residue submitted to 5% aq $HClO_4$ (10 ml) in THF (40 ml) for 12h at rt to hydrolyse the unwanted product of O-alkylation. The THF was removed and the residue partitioned in between ether (100 ml) and cold H_2O (30 ml). The layers were separated and the aq solution extracted with ether (3 x 15 ml). The combined organic extracts was washed with cold H_2O (1 x 30 ml) and brine (1 x 30 ml). Drying and concentration left the crude product which was chromatographed to furnish **1** (9.83 g, 80%).

^{1}H NMR (60 MHz) : ppm 7.1 (s, 5H, Ar-H), 3.63 (s, 3H, CO_2CH_3), 2.8-1.5 (m, 10H, 5xCH_2).

IR (neat), ν_{max} : 1745 (ring C=0), 1715 (CO_2Me) and 1600 cm^{-1}.

3.3.2 Dealkyldecarboxylation of 1

A solution of **1** (1.13 g, 4.6 mmol) in anhydrous DMF (18 ml) was mixed with anhydrous LiCl (0.39 g, 9.2 mmol). The resultant was heated to 145-150 ^oC under N_2 for 10 h, cooled to rt and poured into cold 5% aq $NaHCO_3$ solution (75 ml) and extracted with petroleum ether (40-60) (3x50 ml). The combined extracts was washed with brine (1x25 ml), dried and concentrated. Chromatographic purification gave *2-(2-phenylethyl)cyclopentanone* **3** (0.78 g, 90%).

^{1}H NMR (60 MHz) : ppm 7.1 (s, 5H, Ar-H), 2.6 (bt, 2H, J = 7 Hz, $PHCH_2$-), 2.32-1.21 (m, other hydrogens).

IR (neat), ν_{max} : 1725 (ring C=0) and 1600 cm^{-1}.

Analysis calcd.for $C_{13}H_{16}O$: C, 82.98, H, 8.51;

Found : C, 83.10, H, 8.32%.

3.3.3 Baeyer-Villiger Oxidation of 3

To an ice-cold stirred solution of **3** (0.23 g, 1.22 mmol) in $CHCl_3$ (8 ml) was added perbenzoic acid (0.422 g, 3.0 mmol); 1.4 ml of a 30% solution in $CHCl_3$). This was allowed to come to rt and stirred for 70h. The reaction mixture was poured into saturated aq Na_2SO_3 solution (5 ml), stirred for 30 min anddiluted with cold H_2O (10 ml) and $CHCl_3$ (25 ml). The layers were separated and the aq layer extracted with $CHCl_3$ (3x10 ml). The combined extracts was washed with 10% aq $NaHCO_3$ solution (2x15 ml) and brine (1x15 ml), dried and concentrated. Chromatography of the crude residue afforded *6-(2-phenylethyl) tetrahydropyran-2-one* **4** (0.236 g, 95%):

^1H NMR (60 MHz) : ppm 7.1 (s, 5H, Ar-H), 4.15 (m, 1H, -COOCH-), 2.7 (t, 2H, J = 8 Hz, $PhCH_2$-), 2.3 (bd, 2H, J = 6 Hz, $-COCH_2$), 2.1-1.1 (m, 6H, $3xCH_2$).

IR (neat), ν_{max} : 1730 (lactone C=0) and 1600 cm^{-1}.

Mass (m/z) : 205 (M^++1), 204 (M^+)

Analysis calcd.for $C_{13}H_{16}O_2$: C, 76.47, H, 7.84;

Found : C, 76.18, H, 7.74%.

3.3.4 Selenenation of 4

A flame dried 2-necked rb flask equipped with magnetic stirrer and a rubber septum was charged, under N_2, with dry THF (2 ml) and diisopropylamine (0.163 g, 1.58 mmol). The content was

cooled to -80 ^{o}C and treated with n-BuLi (1.05 ml of 1.5M solution in hexanes, 1.57 mmol). After 10 min, a solution of **4** (0.27 g, 1.32 mmol) in THF (3 ml) was added dropwise (5 min) and resultant stirred for 30 min.

Meanwhile, a solution of diphenyldiselenide (0.25 g, 0.78 mmol) in THF (0.5 ml) was mixed with a solution of Br_2 (0.14 g, 0.78 mmol) in THF (0.5 ml) at 5 ^{o}C for 15 seconds. This dark colored benzeneselenenyl bromide was now injected,all at once,into the above yellow colored enolate solution. Immediate decoloration took place. The reaction mix was stirred at -80 ^{o}C for 2h and allowed to come slowly (4h) to rt. The reaction solution was poured into ice-cold mix of 10% aq HCl (10 ml) and ether-petroleum ether combine (1:1, 10 ml). The layers were separated and the organic layer washed with cold H_2O (1x5 ml), cold 5% aq $NaHCO_3$ (1x5 ml), and brine (1x5 ml), in that order. This was dried and concentrated to leave a residue that was chromatographed to furnish *3-benzeneselenenyl-6-(2-phenylethyl)tetrahydropyran-2-one* 5 (0.45 g, 95%).

^{1}H NMR (80 MHz) : ppm 7.8-7.46 (m, 2H, SePh *meta*-H), 7.4-7.0 (m, 8H, SePh *ortho* & *para*-H), Ar-H), 4.3 (m, 1H, -COOCH-), 4.15-3.8 (m, 1H, PhSeCH), 3.0-2.7 (m, 2H, $PhCH_2$-), 2.4 - 1.3 (m, 6H, 3 x CH_2)

IR (neat), ν_{max} : 1715 (lactone C=0), 1590 and 1565 cm^{-1}.

Mass (m/z) : 359 (M^+).

3.3.5 Dehydroselenation of 5

To a stirred solution of selenolactone **5** (0.36 g, 1.0 mmol)

and pyridine (0.158 g, 2.0 mmol) in CH_2Cl_2 (5 ml) was added H_2O_2 (350 µl of a 30% aq H_2O_2 mixed with 700 µl of distilled H_2O) dropwise at 0^oC. After complete addition, the reaction mix was stirred at this temperature for 20 min and at rt for another 20 min. The reaction mix was poured into a cold mix of CH_2Cl_2 (20 ml) and 5% aq $NaHCO_3$ (20 ml) and stirred for 5 min. The layers were separated and the aq solution extracted with CH_2Cl_2 (2x10 ml). The combined organic exdtracts was washed successively with cold 5% aq HCl (1x15 ml) and brine (1x15 ml). Drying and solvent removal furnished a residue which was chromatographed to deliver *3,4-dehydro-6-(2-phenylethyl)tetrahydropyran-2-one* **6** (0.19 g, 94%).

^{1}H NMR (60 MHz) : ppm 7.15 (s, 5H, Ar-H), 7.0-6.6 (m, 1H, -CH=CH-C(O)-), 5.95 (qd, 1H, J = 12.5 Hz, -CH=CH-C(O)-), 4.35 (m, 1H, -COOCH), 3.0-2.55 (m, 2H, $PHCH_2$-), 2.5-1.6 (m, 4H, 2xCH_2).

IR (neat), ν_{max} : 1720 (enelactone C=0) and 1610 cm^{-1}.

Mass (m/z) : 203 ($M^+ + 1$), 202 (M^+).

Analysis calcd.for $C_{13}H_{14}O_2$: C, 77.23, H, 6.93;
Found : C, 77.35, H, 7.02%.

3.3.6 Dibal-H reduction of enelactone 6

To a solution of **6** (0.125 g, 0.62 mmol) in dry DME (5.5 ml) and dry toluene (10 ml) was added, under N_2 and at -80 ^oC, a toluene solution of Dibal-H (575 µl of a 20 wt% solution in toluene, 0.81 mmol) dropwise over a period of 10 min. The solution was stirred for 30 min and saturated aq $NaHCO_3$ (4.5 ml)

added. The mix was stirred at -80°C for 15 min and then allowed to warm to rt after removing it from the cooling bath. 30 Min later, H_2O (18 ml) was added and most of the toluene and other organic solvents removed *invacuo*. The residue was extracted with EtOAc (3 x 15 ml) which was dried and concentrated.Chromatographic purification afforded the product *3,4-dehydro-2-hydroxy-6-(2-phenylethyl)tetrahydropyran* **7** (0.126 g, 100%).

^{1}H NMR (80 MHz) : ppm 7.2 (s, 5H, Ar-H), 6.2-5.6 (m, 2H,, -HC=CH-), 5.41 (bs, 1H, -OCH(OH)), 3.94 (m, 1H, -OCH-), 2.6 (m, 3H, $PhCH_2$-, -OH), 2.15-1.5 (m, 4H, 2xCH_2).

IR (neat), ν_{max} : 3420 (OH), 1715 and 1610 cm^{-1}.

Mass (m/z) : 204 (M^+).

3.3.7 Diastereoselective epoxidation of enelactone 6

To a solution of DBU (0.186 g, 1.2 mmol) and anhydrous *t*-BuOOH (0.85 ml of 2.35 M solution in dichloroethane, 2.0 mmol) in dry dichloroethane (3 ml) was added a dichloroethane solution (2 ml) of enelactone **6** (0.202 g, 1 mmol) at 5°C and the resultant stirred at rt for 12 h. The volatiles were removed *in vacuo* and residue chromatographed to give *3,4-epoxy-6-(2-phenylethyl)tetrahydropyran-2-one* **9** (0.165, 75%).

^{1}H NMR (400 MHz) : ppm 7.37-7.15 (m, 5H, Ar-H), 4.53 (m,1H, -COOCH-), 3.62 (m, 1H, oxirane-H, β to carbonyl), 2.9-2.8 (m, 1H, PhCH-), 2.8-2.65 (m,1H, PhCH-), 2.35 (td, 1H, J = 12, 3Hz, oxirane-H, α to carbonyl), 2.07-1.77 (m, 4H, 2 x CH_2).

IR (neat), ν_{max} : 1710, 1600, 1240, 1160, 1020 and 900 cm^{-1}.

Mass (m/z) : 219 (M^++1), 218 (M^+).

Analysis calcd.for $C_{13}H_{14}O_3$: C, 71.56, H, 6.42;

Found : C, 71.46, H, 6.30%.

3.3.8 Regioselective cleavage of oxirane ring of epoxy lactone 9

To a solution of **9** (0.109 g, 0.5 mmol) in 2-butanone (5 ml) was added anhydrous NaI (0.375 g, 2.5 mmol) and the resultant refluxed for 5h. The volatiles were removed and residue taken in ether (15 ml). This was washed with saturated aq sodium thiosulphate (2x5 ml) and brine (1x5 ml), dried, filtered and concentrated to furnish the crude product. Chromatographic purification gave *4-hydroxy-6-(2-phenylethyl)tetrahydropyran-2-one* **12** (0.094 g, 85%).

^{1}H NMR (400 MHz) : ppm 7.36-7.15 (m, 5H, Ar-H), 4.71 (m, 1H, -COOCH-), 4.4 (quintet, 1H, -CH(OH)), 2.96-2.84 (m, 1H, PhCH-), 2.80-2.70 (m, 2H, PhCH-, -C(O)CH(ax)-), 2.63 (dd, 1H, J = 18 and 3.5 Hz, -C(O)CH(eq)-), 2.1-1.85 (m, 4H, $PhCH_2CH_2$-, -CH(OH)CH(ax)-), 1.80 (ddd, 1H, 12, 10 and 3 Hz, -CH(OH)CH(eq-).

IR (neat), ν_{max} : 3420 (OH), 1710 (lactone C=0) and 1590 cm^{-1}.

Mass (m/z) : 221 (M^++1), 220(M^+).

Analysis calcd.for $C_{13}H_{16}O_3$: C, 70.90, H, 7.27;

Found : C, 70.98., H, 7.31%.

3.3.9 Acetylation of 12

To a solution of β-hydroxy valerolactone **12** (0.028 g, 0.127

solution of racemic acetates **13** (0.03 g, 0.114 mmol) in ether (1 ml) followed by PLAP (60 mg), at 10 - 15 ^{o}C, with good stirring. After 48h, the reaction was quenched with 2N HCl (0.4 ml) to accomplish the pH 6.5 of the reaction mixture. To this, NaCl (0.2 g) and EtOAc (5 ml) were added and the resulting suspension was vigorously stirred for 15 min. The enzyme was removed by filtration under suction and layers were separated. The aq layer was extracted with EtOAc (3 x 4 ml) and the combined organic layer washed with brine (1 x 4 ml), dried and concentrated. Chromatographic purification gave 8 mg of inseparable mixture of unreacted acetate **13a** and eneleactone **6** in the ratio 4:6 (^{1}H NMR) and optically active alcohol **14** (0.01 g, 86%) [$[\alpha]_D^{25}$ = - 42.5^{o} (c = 10 mg/2 ml $CHCl_3$)].

Other spectral data are identical to that of **12** (expt. 3.3.8).

Based on rotation [cf lit[11]. $[\alpha]_D^{25}$ = -45.2^{o} (c = 0.44, $CHCl_3$)], **14** is computed to be of 94% ee.

3.3.12 Preparation of MTPA ester of optical active alcohol 14:

To a solution of alcohol **14** (2 mg, 0.01 mmol) in anhydrous CH_2Cl_2 (500 μl) was added, at 0 ^{o}C and under N_2, pyridine (2.37 mg, 0.03 mmol), one small crystal of DMAP and (R)-(+)-MTPA-Cl (5.0 mg, 0.02 mmol). The resultant was stirred at 0 ^{o}C for 10 h. Dichloromethane was removed and the residue chromatographed to give 2 mg of an inseparable mix of **MTPA-14** and enelactone **6(S)-6** in the ratio 6:4.

^{1}H NMR spectrum of MTPA-14 : ppm 7.5-7.1 (m, 10H, Ar-H), 5.50 (bs, 1H, -C(OMe)(CF_3)C(O)OCH-), 4.42 (m, 1H, -(O)COCH-), 3.50 (s, 3H, -OCH_3).

3.3.13 General experimental procedure for etherification of enelactol 7

To an ice-cold solution of **7** (0.071 g, 0.348 mmol) and the requisite alcohol (0.55 mmol) in dry ether (5 ml) was added, under N_2, $BF_3.OEt_2$ (0.074 g, 0.52 mmol). The resultant reaction mix was stirred for 20 h at 20 ^oC and poured into saturated aq $NaHCO_3$ (3 ml). The layers were separated and the aq layer extracted with ether (3 x 5 ml). The combined ethereal extracts was washed with brine (1 x 5 ml), dried, and concentrated. The residue, so obtained, was chromatographed to furnish the product (80%).

3,4-Dehydro-2-methoxy-6-(2-phenylethyl)tetrahydropyran **18**

^{1}H NMR (60 MHz) : ppm 7.1 (s, 5H, Ar-H), 6.0-5.4 (m, 2H, -HC=CH-), 4.7 (bs, 1H, -OCH(OMe)-), 4.1-3.5 (m, 1H, -OCH-), 3.4 (s, 3H, OCH_3), 3.0-2.45 (m, 2H, $PhCH_2$-), 2.1-1.5 (m, 4H, 2xCH_2).

IR (neat), ν_{max} : 1600 and 1450 cm^{-1}.

Mass (m/z) : 218(M^+).

3,4-Dehydro-2-ethoxy-6-(2-phenylethyl)tetrahydropyran **27**

^{1}H NMR (60 MHz) : ppm 7.2 (s, 5H, Ar-H), 6.2-5.4 (m, 2H, -HC=CH-), 4.83 (bs, 1H, -OCH(OEt)-), 4.1-3.1 (m, 3H, $-OCH_2CH_3$, -OCH-), 3.0-2.4 (m, 2H, $PhCH_2$-), 2.1-1.5 (m, 4H, 2xCH_2), 1.1 (t, 3H, J=7 Hz, OCH_2CH_3).

IR (Neat), ν_{max} : 1600 and 1400 cm^{-1}

Mass (m/z) : 232 (M^+).

3.3.14 Sharpless asymmetric epoxidation of enelactol 7

To a solution of enelactol **7** (0.01 g, 0.05 mmol) and vanadyl acetylacetonate (1 mg) in dry benzene (2 ml) was added anhydrous *t*-BuOOH (0.1 mmol, 42 μl of 2.35 M solution in dichloroethane). The resultant mix was refluxed for 3h and cooled to rt. Saturated aq Na_2SO_3 (2 mL) was added to the reaction mix, stirred for 15 min and partitioned between EtOAc (10 ml) and H_2O (3 ml). The layers were separated and the aq phase extracted with EtOAc (2 x 5 ml). The combined organic extracts was washed with brine (1 x 5 ml). Drying, solvent removal, and chromatography afforded the dimer **15** (0.004 g, 41%).

^{1}H NMR (400 MHz) : ppm 7.35-7.14 (m, 10H, Ar-H), 6.22 (bt, 2H, J = 9Hz, 2 x -HC=CH-HCO-), 5.66 (bdd, 2H, J = 9 and 2 Hz, 2 x - HC=CH-CHO), 5.52 (bs, 2H, 2 x acetal-H), 3.94 (m, 2H, 2x -OCH-), 2.87 (m, 2H, 2 x PhCH-), 2.67 (m, 2H, 2 x PhCH-), 2.1 - 1.8 (m, 8H, 4 x CH_2).

IR (neat), ν_{max} : 1650, 1590, 1490, 1450, 1180 and 1110 cm^{-1}.

Mass (m/z) : 390 (M^+).

Analysis calcd.for $C_{26}H_{30}O_3$: C, 80.00, H, 7.69;
Found : C, 79.78, H, 7.34%.

3.3.15 Reaction of dimer 15 with MeOH and Conc. HCl (catalyst)

A solution of the dimer **15** (0.070 g, 0.179 mmol) in dry MeOH (4 ml) and a catalytic amount of conc. HCl was refluxed for 6h. The reaction mix was cooled to rt and freed of the solvent. The residue was taken up with ether (10 ml) and saturated aq $NaHCO_3$ (3 ml). The layers were separated and the aq layer

extracted with ether (4 x 5 ml). The combined ether extracts was washed with cold H_2O (2 x 7 ml) and brine (1 x 7ml), dried, and concentrated to furnish, after chromatography, the diastereomeric mixture of *2,4-dimethoxy-6-(2-phenylethyl)tetrahydropyrans* **19a** *and* **19b** (0.085 g, 95%) in 84:16 ratio.

^{1}H NMR (400 MHz) of 19a : ppm 7.31-7.2 (m, 5H, Ar-H), 4.6 (dd, 1H, J = 10 and 2.5 Hz, OCH(OMe)-), 3.79-3.66 (m, 2H, -OCH-, -CH(OMe)-), 3.56 (s, 3H, -OCH(OCH$_3$)-), 3.3 (s, 3H, -OCH$_3$), 2.85 (m, 1H, PhCH-), 2.68 (m, 1H, PhCH-), 2.39 (bqd, 1H, J = 13 and 2.5 Hz H(eq) at position 3), 1.89 (m, 1H, H(ax) at position 3), 1.7-1.58 (m, 2H, 1 x CH$_2$, ring), 1.46 (m, 1H, PhCH$_2$-CH-), 1.35 (m, 1H, PhCH$_2$-CH-).

^{1}H NMR (400 MHz) of 19b : ppm 4.87 (bs, 1H, OCH(OMe)-), 3.31 (s, 3H,-OCH$_3$ at position 4) with other characteristics peaks similar to that of **19a**.

IR of 19(a,b) (neat), ν_{max} : 1590, 1480 and 1440 cm^{-1}.

Mass (m/z) of 19 (a,b) : 251 (M^++1), 250 (M^+).

Analysis calcd.for $C_{15}H_{22}O_3$: C, 72.00, H, 8.80;
Found : C, 72.18, H, 8.70%.

3.3.16 Reaction of 27 with MeOH and PPTS catalyst

A solution of **27** (0.019 g, 0.081 mmol) and catalytic amount of PPTS in dry MeOH was refluxed for 3h when the starting material had disappeared completely and new more polar product was formed. The reflux was continued for additional 13 h with no

ange in TLC behaviour. MeOH was removed *in vacuo* and residue ltered through a short silica gel column to afford a material lentical to **18** (cf expt. 3.3.13) both from TLC and from)ectroscopic characteristics (^{1}H NMR, IR).

3.3.17 Acetal hydrolysis of 19 followed by Fetizon oxidation

A solution of **19** (0.025 g, 0.1 mmol) in 3 ml of a 3 : 5 ix of 10% aq HCl and THF was stirred at 45 ^{o}C and under N_2 for 75 in. The reaction mix, after cooling to rt, was taken up in 60 ml f ether and washed with a saturated aq $NaHCO_3$ (1 x 10 ml). The q phase was extracted with ether (2 x 25 ml). The combined ether xtracts was washed with brine (1 x 15 ml), dried and concentrated n *vacuo* to afford 0.028 g of a mix of lactols which were used irectly in the next reaction.

To a solution of above lactols in dry benzene (10 ml) was dded Ag_2CO_3 (1.0 mmol, 0.58 g of 48% by weight on celite). The esultant heterogeneous reaction mix was refluxed, in dark and nder N_2, for 5h, cooled to rt, and filtered through a pad of elite with thorough washing with ether (50 ml). Concentration of he filtrate and chromatography of the residue furnished *l-methoxy-6-(2-phenylethyl)tetrahydropyran-2-one* **20a** and **20b** (0.02 g, 86%) as a 84 : 16 mix of diastereoisomers (^{1}H NMR).

^{1}H NMR (400 MHz) of 20a : ppm 7.35-7.14 (m, 5H, Ar-H), 4.55 (m, 1H, -COOCH-), 3.76 (quintet, 1H, -HC(OMe)-), 3.30 (s, 3H, $-OCH_3$), 2.85 (m, 1H, PhCH-), 2.80-2.65 (m, 3H, PhCH-, $-H_2CC(O)-$), 2.04 (bqd, 1H, J = 15.5 Hz, H(eq) at position 5), 2.0 (m, 1H, $PhCH_2CH$-),

1.87 (m, 1H, $PhCH_2C\underline{H}$-), 1.57 (ddd, 1H, J = 15.5, 8 and 4 Hz, $\underline{H}$(ax) at position 5).

^{1}H NMR (400 MHz) of 20b : ppm 4.14 (m, 1H, -COOC$\underline{H}$-), 3.71 (m, 1H, -$\underline{H}$C(OMe)-), 3.32 (s, 3H, -OC$\underline{H}_3$) with other characteristic peaks similar to that of **20a**.

IR of 20(a,b) (neat), ν_{max} : 1735 (lactone C=0) and 1590 cm^{-1}.

Mass (m/z) of 20(a,b) : 234 (M^+).

Analysis calcd.for $C_{14}H_{18}O_3$: C, 71.79, H, 7.69;

Found : C, 71.61, H, 7.47%.

3.3.18 Demethylation of methoxy valerolactone 20

To a solution of methyl ether **20** (0.01 g, 0.043 mmol) in dry CH_2Cl_2 (500 μl) at -80 ^oC under argon was added BBr_3 (300 μl of 1.0 M solution in CH_2Cl_2, 0.3 mmol). After 10 min, the reaction mixture was warmed to -20 ^oC and stirred there for 5 h. The reaction mixture was quenched by addition of dry ether (2 ml) followed by the addition of the mixture, via cannula, to a stirred cooled (0 ^oC) solution of saturated aq $NaHCO_3$ (10 ml). After 5 min the reaction solution was extracted thoroughly with ether (4 x 25 ml). The combined ether extracts was dried, freed of volatiles, and concentrated to give a residue which,after chromatographic purification, gave an 84:16 mix of diastereomeric alcohols **12a** and **12b** (4.5 mg, 45%) [cf. expt. 3.3.8].

Fig. 3.1 ^{1}H NMR spectrum (60 MHz) of **6**

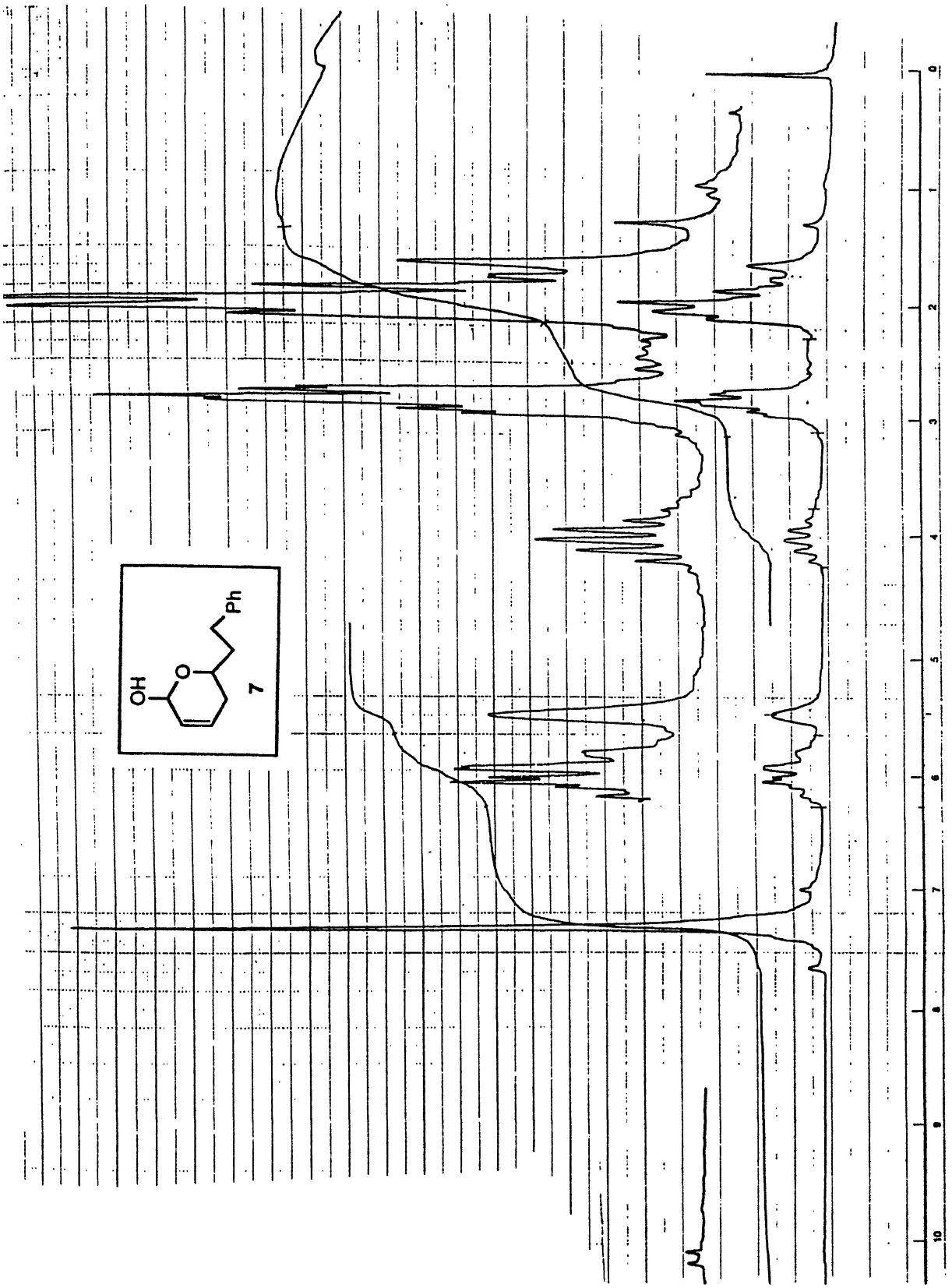


Fig. 3.2 ^{1}H NMR spectrum (80 MHz) of **7**

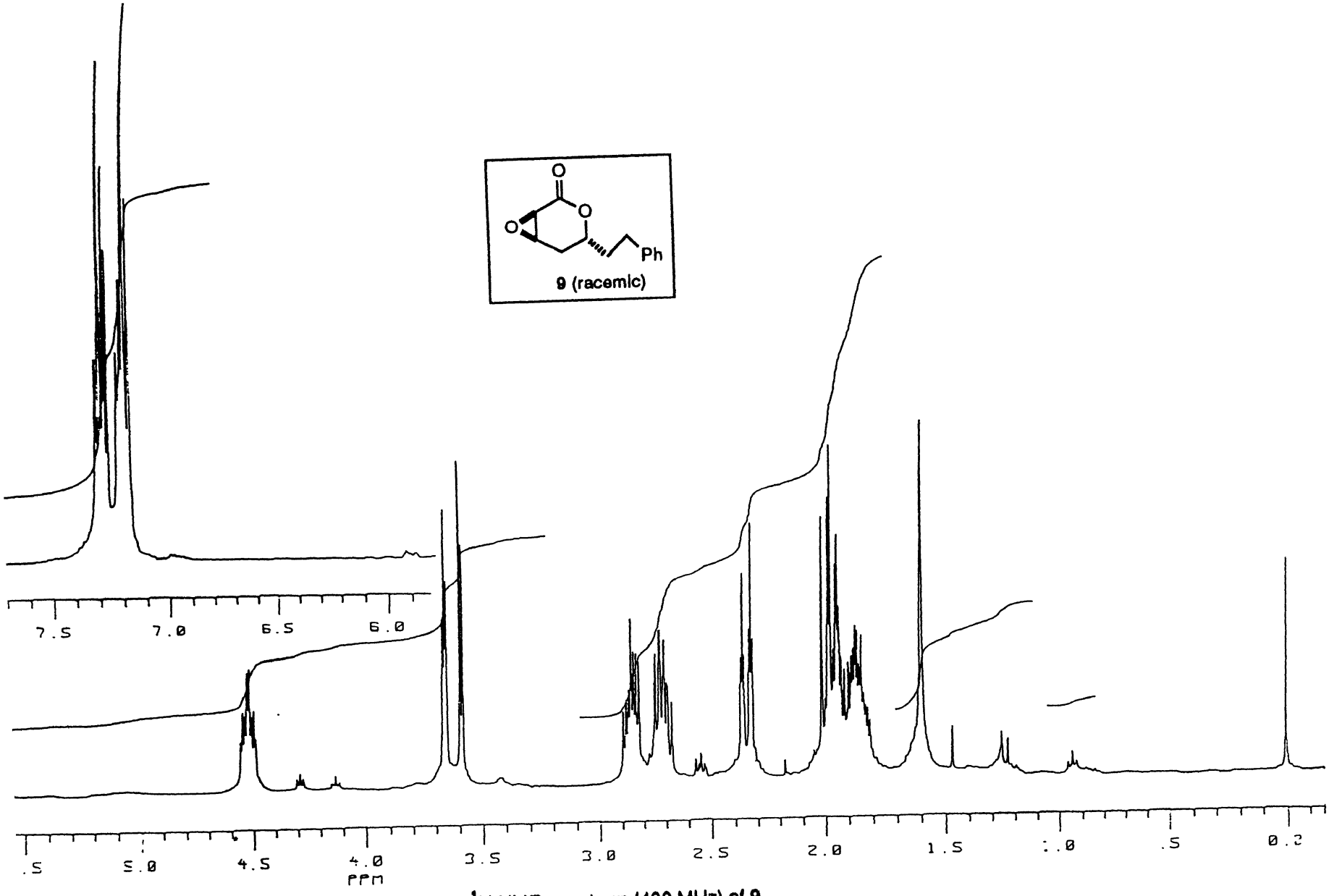


Fig. 3.3 ^{1}H NMR spectrum (400 MHz) of **9**

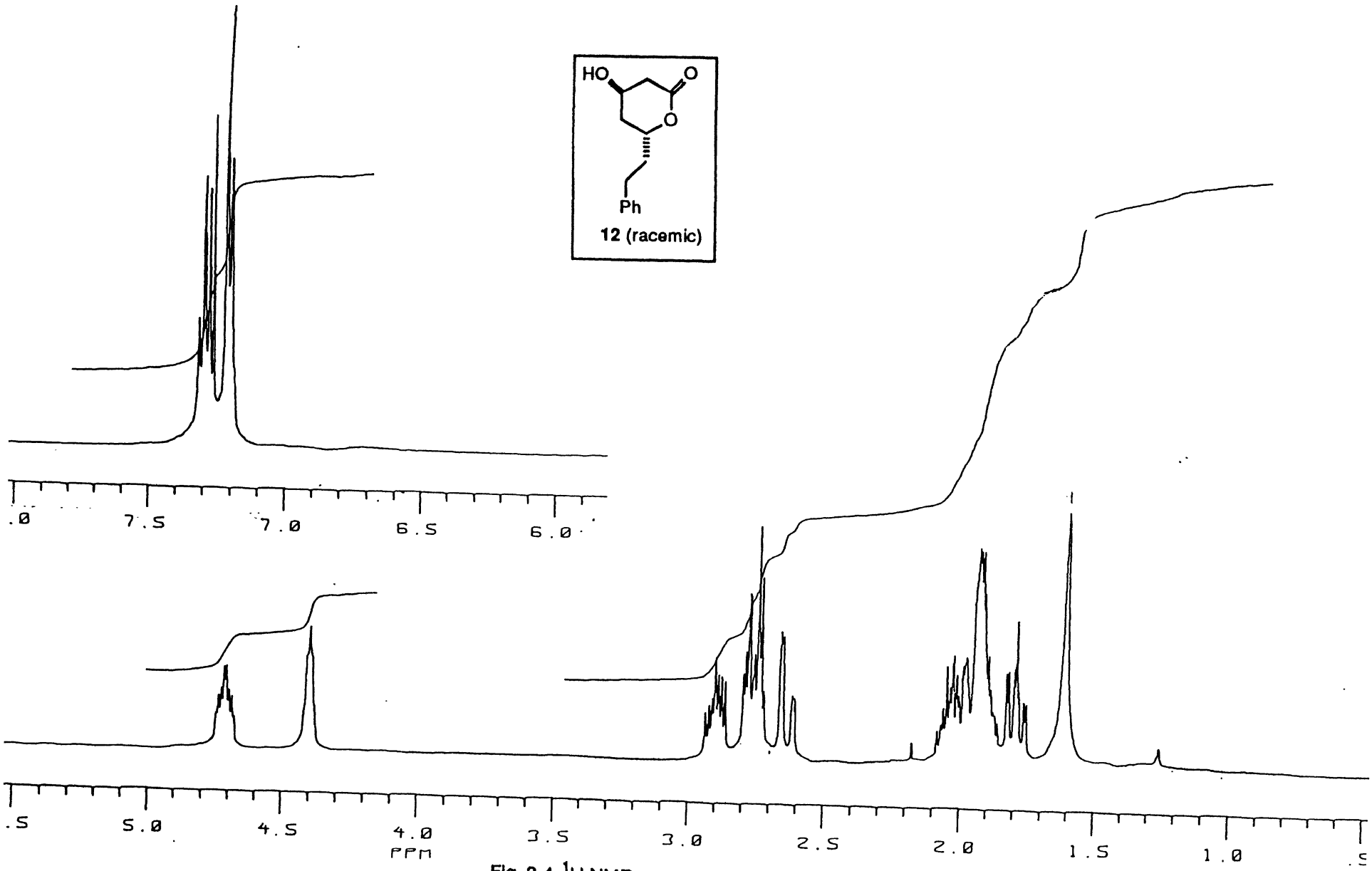


Fig. 3.4 ^{1}H NMR spectrum (400 MHz) of **12**

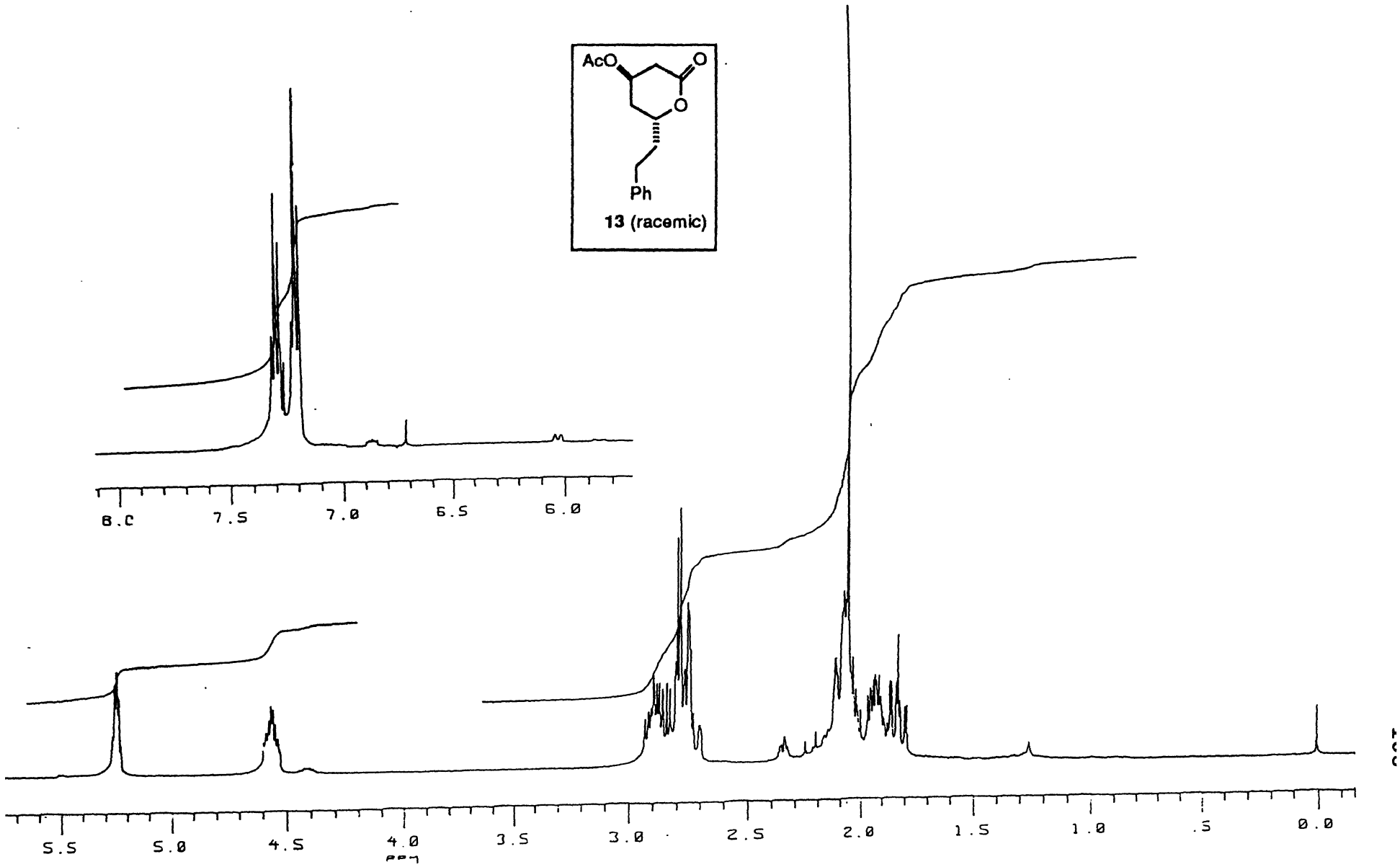


Fig. 3.5 ^{1}H NMR spectrum (400 MHz) of **13**

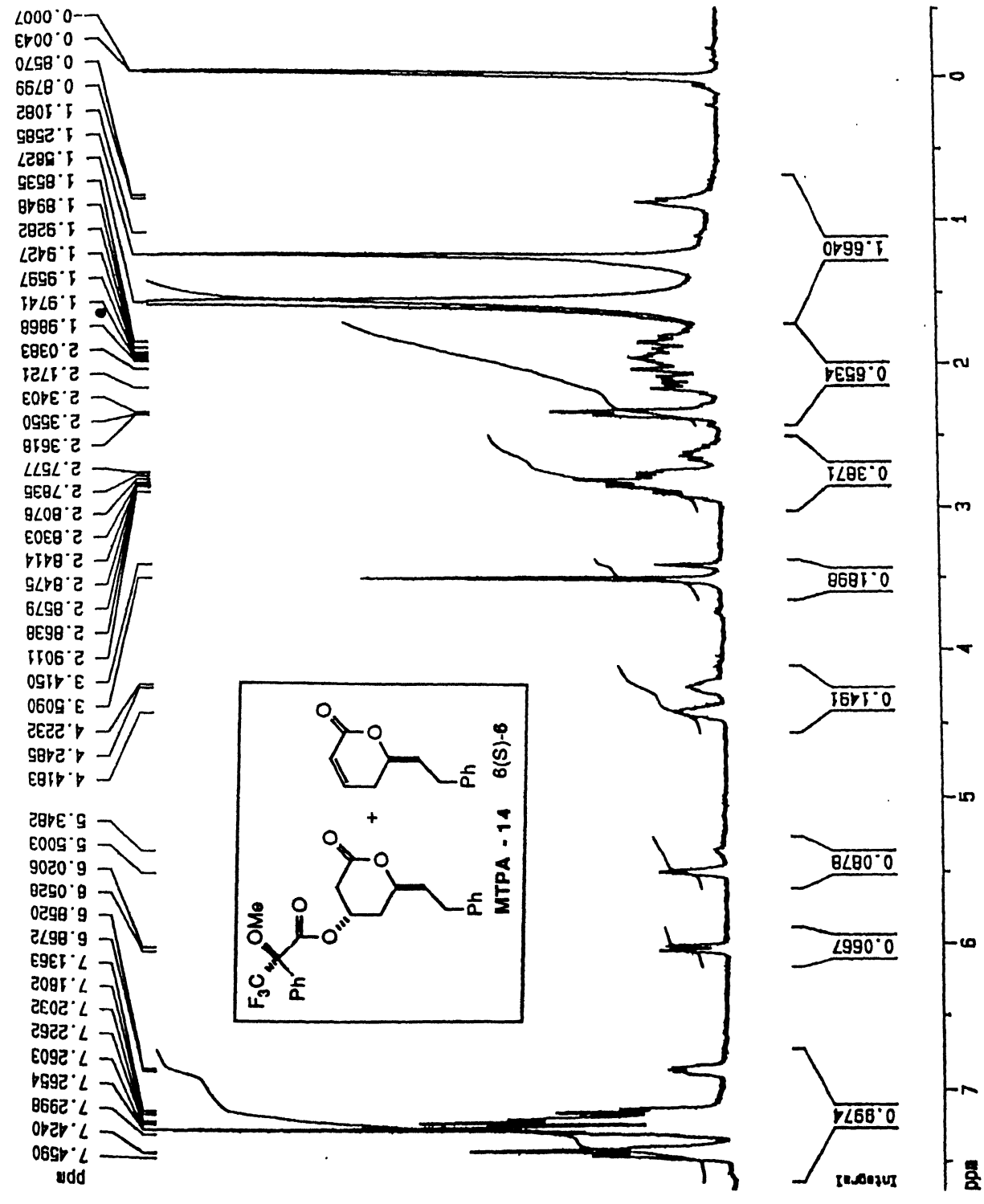


Fig. 3.6 ^{1}H NMR spectrum (300 MHz) of **MTPA - 14 & 6(S)-6**

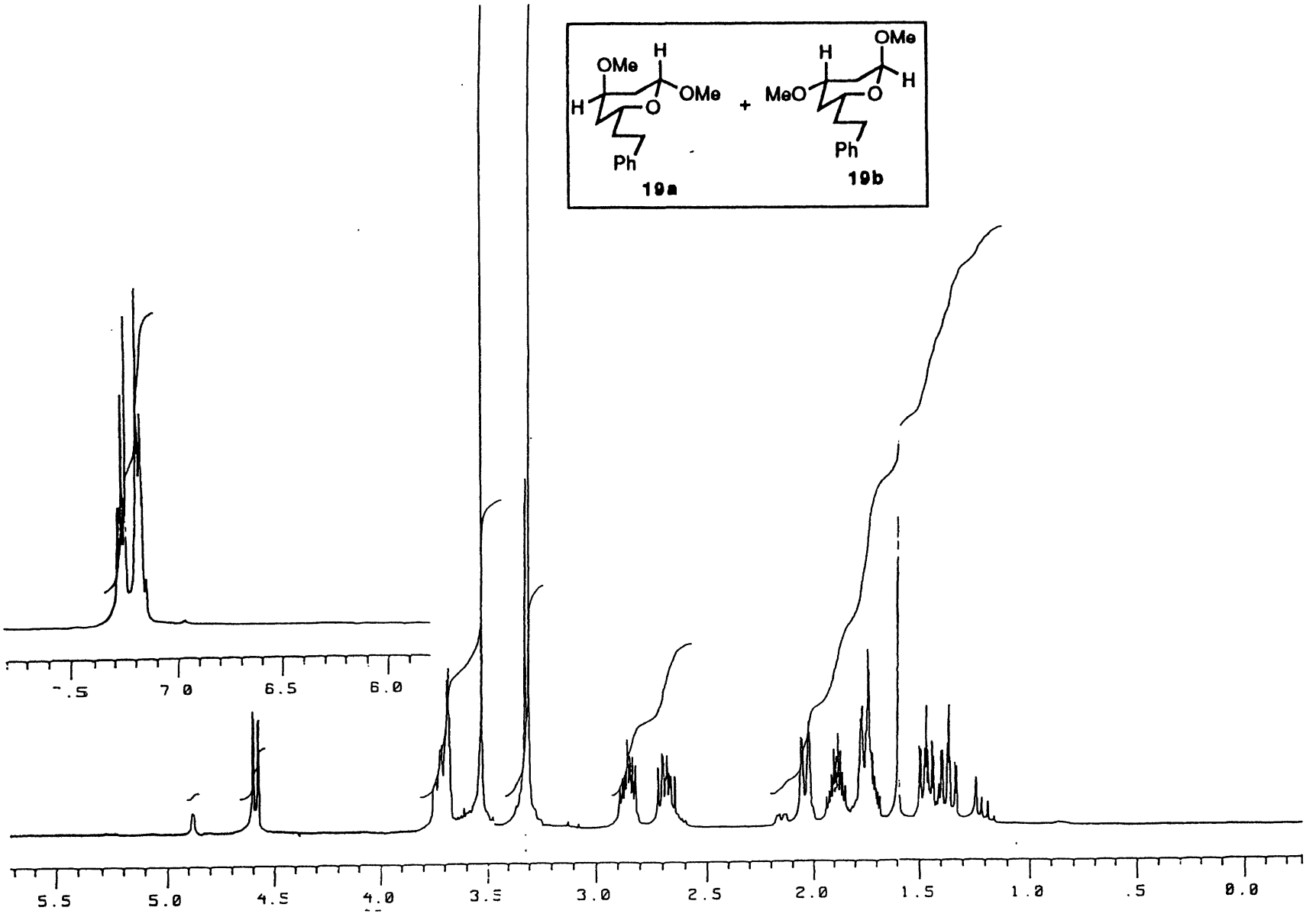


Fig. 3.7 ^{1}H NMR spectrum (400 MHz) of 19(a,b)

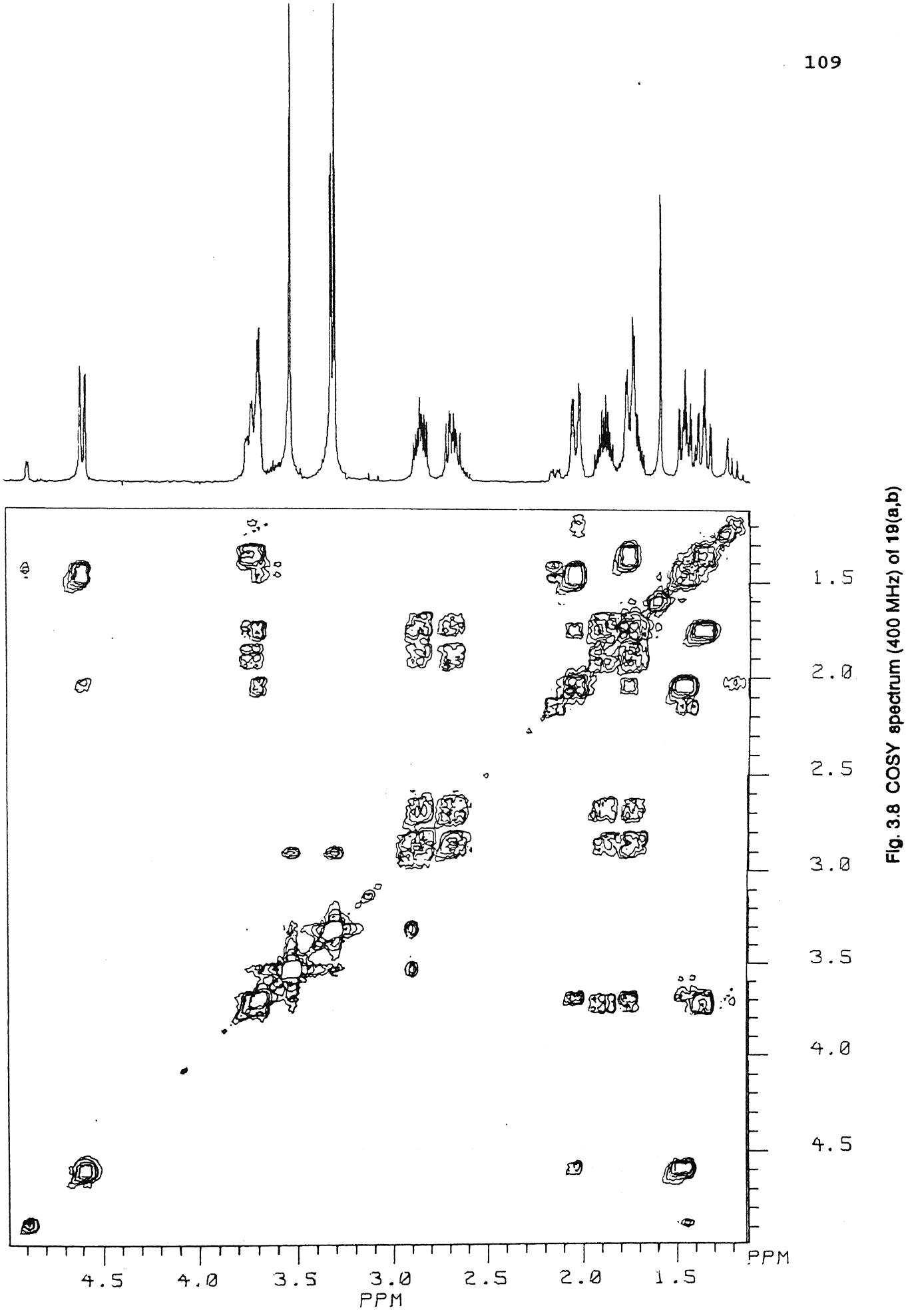


Fig. 3.8 COSY spectrum (400 MHz) of 19(a,b)

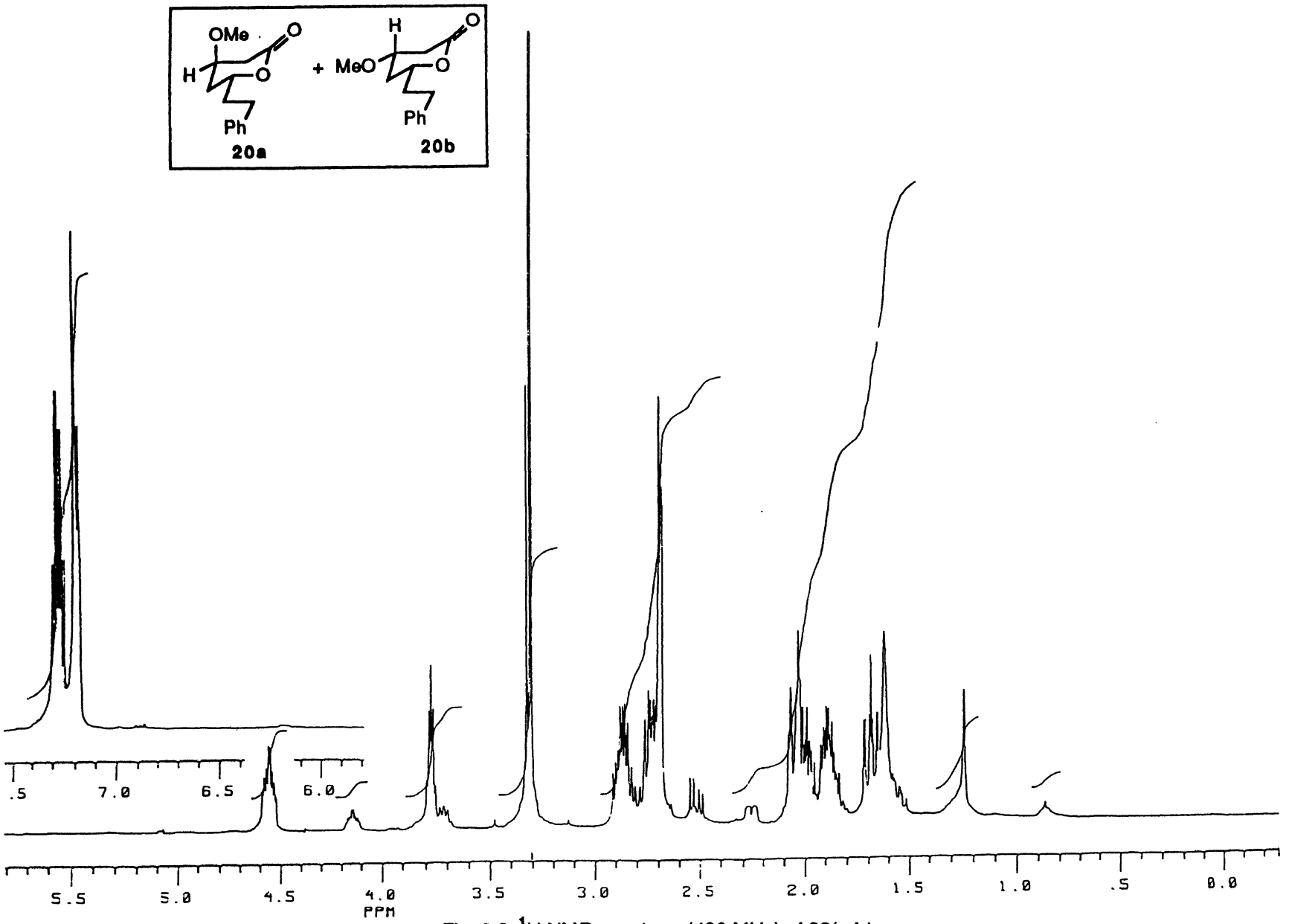


Fig. 3.9 ^{1}H NMR spectrum (400 MHz) of 20(a,b)

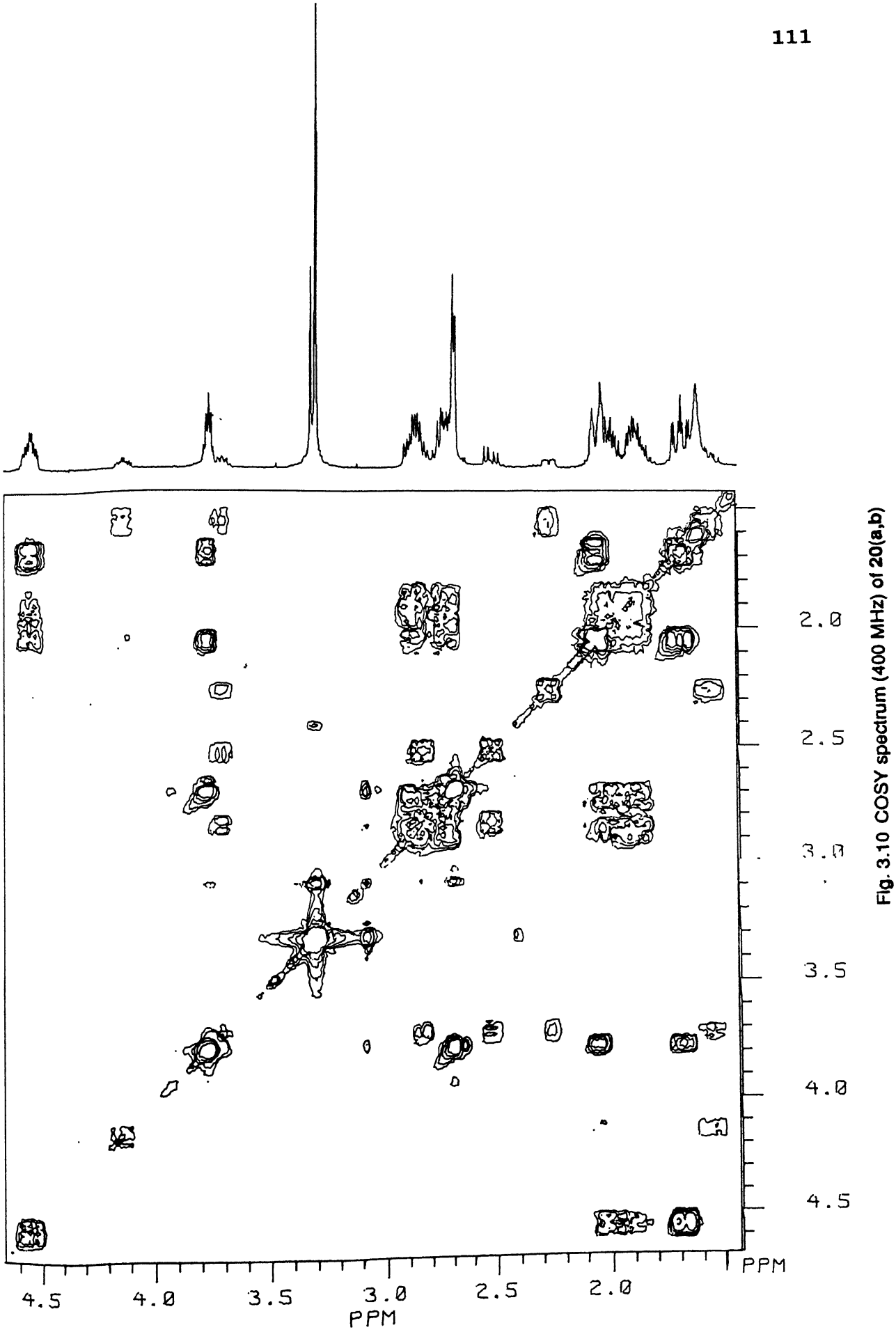


Fig. 3.10 COSY spectrum (400 MHz) of 20(a,b)

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NEWER OXIDATION REAGENTS

(a) t-BuOOH and KF-impregnated Al_2O_3

(b) t-BuOOH and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)

4.1 Introduction

Epoxidation of electron-deficient alkenes is an important reaction. The resulting epoxy materials are readily transformed into various useful targets including, e.g. α- and β-hydroxy carbonyl compounds[1], α,β-epoxy alcohols[2], allylic alcohols[3], 1,3-diols[4a], and 1,3-diketones[4b]. Nucleophilic α- and β-openings of the oxirane ring, whether or not under the influence of suitable additives, enhance their utility further[5]. β-Hydroxy ketones (aldols) are useful materials as they have been found to act as key intermediates in the synthesis of a variety of natural products, e.g. cardiac active steroids[6] like periplogenin and strophanthidin.

The α- and β-hydroxy carbonyl groupings are present in various natural products including mevinolins. The bulk activity of mevinolins is due to the β-hydroxy-δ-lactone unit, the role of decalin segment is purely that of hydrophobic in nature and provides the necessary guidance for suitable interaction with the active site of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase[7]. Davis reagent, the oxirane derived from N-(p-toluenesulphonyl)benzylimine, is an useful material for the convenient introduction of a hydroxyl function α to a carbonyl group[8]. In connection with a programme aimed at the synthesis of mevinolin analogs, we became interested in the epoxidation of 6-(2-phenylethyl)-3,4-dehydrotetrahydropyran-2-one **20**. A brief review on the epoxidation of electron deficient olefins is presented below.

Payne and Williams[9] epoxidised α,β-unsaturated ketones, and sulfones utilising alkaline H_2O_2.

Danishefsky[10] employed this methodology to carry out the epoxidation of an α-methylidene-δ-lactone in the synthesis of dl-pentaleno lactone. α,β-Unsaturated esters can be epoxidised with mCPBA in dichloroethane at reflux[11].

Epoxidation at elevated temperature is associated with thermal radicalar decomposition of peracids. Kishi et al[12] investigated the possibility of suppressing the thermal decomposition of mCPBA in dichloroethane at 90 °C in presence of radical inhibitors. The results are given in the following table. It is evident that the decomposition is suppressed in the presence of some radical inhibitors, the best of which is 4,4'-thiobis-(6-t-butyl-3-methylphenol). Although 4,4'-thiobis-(6-t-butyl-3-methylphenol) appears to be the best to inhibit the said decomposition, it is less readily available. The next inhibitor of choice may be 2,6-di-t-butyl-4-methylphenol.

Table : Decomposition of mCPBA in the presence of radical inhibitor[a]

Radical inhibitor	Peracid remaining[b] (%) after 1h heating	after 3h heating
4,4'-Thiobis-(6-t-butyl)-3-methylphenol)	100	100
2,6-Di-t-butyl-4-methylphenol	90	77
4,4'-Butyldienebis-(6-t-butyl-3-methyl-phenol)	91	20
Dilauryl 3,3'-thiodipropionate	93	<10
Distearyl 3,3'-thiodipropionate	55	<10
Hydroquinone	~30	---
None	27	---

[a]mCPBA (20 mg) was heated at 90 °C in dichloroethane (2.0 ml) containing 0.2 mg inhibitor. [b]Determined iodometrically.

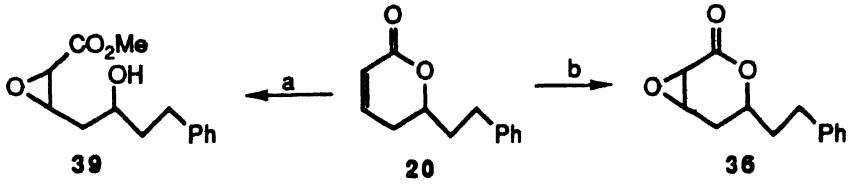
t-BuOOH in combination with bases such as Triton-B[13] and KH[14] and potassium t-butoxide[15] have been employed successfully to

bring the epoxidation of electrophilic olefins. Whereas the first two combinations have been attempted on enones only, the last one is succesful with both the enones and the α,β-unsaturated esters. Alkylzinc alkylperoxides[16] are very chemoselective and bring about epoxidation of enones only. Lithium t-butylhydroperoxide, generated by the addition of alkyl lithiums to anhydrous t-butyl hydroperoxide in THF solution, is reported[17] to oxidise electrophilic alkenes, e.g. α,β-unsaturated esters, sulfones, sulfoximines, and amides at -20 ^{o}C with complete regio- and stereospecificity. When used in presence of appropriate chiral auxilliaries, this reagent exhibits some chiroselectivity (20-100%) as well. Julia et al[18] succeeded in achieving almost complete stereospecific epoxidation of chalcone by means of a triphasic catalytic system using 'synthetic enzymes'. These enzymes are readily available syhnthetic chiral polypeptides such as poly[(S)-alanine]. The other two phases were that of toluene and alkaline aqueous H_2O_2.

4.2 Results and Discussion

Attempted epoxidation of 3,4-dehydro-6-(2-phenylethyl)-tetrahydropyran-2-one **20** with alkaline H_2O_2 in MeOH under

Scheme 4.2.1



trans : cis = 6 : 4 ; non-separable by column chromatography

(a) H_2O_2, $NaHCO_3$, MeOH ; 20% (b) mCPBA, dichloroethane, reflux ; 60% conversion

conditions related to those of Danishefsky[10] was very slow. Lactone ring opening was prominent and methyl 2,3-epoxy-5-hydroxy--7-phenyl-2-heptenoate **39** was the major product isolated (Scheme 4.2.1). The compound **39** analysed correctly for $C_{14}H_{18}O_4$ and showed in its mass spectrum the highest mass peak at m/z 250, which is consistant with its molecular formula. The IR spectrum was quite informative and revealed the nature of the functional groups. Thus, the presence of a hydroxy group (3480 cm^{-1}) and the epoxy ester (1730, and 1270, 900 and 750 cm^{-1}) are clearly indicated by diagnostic IR bands. ^1H NMR spectrum further confirms the structure assigned to **39** (cf expt. 4.3.1). Replacement of MeOH by other water-miscible and yet non-nucleophilic solvents such as THF and DME did not promote any reaction.

Biphasic reaction in benzene and water with $H_2O_2/NaHCO_3/n\text{-}Bu_4NI$ was ineffective. The reaction using Triton-B[13] in benzene was very complex; the isolation of any meaningful pure compound proved futile.

Treatment with excess mCPBA (2 equivalents) in dichloroethane[11] at reflux for 6h without any radical inhibitor furnished a mixture of desired oxirane **36** and the unreacted enelactone **20**. Although mCPBA was still present, the conversion to oxirane **36** was only 60% (cf expt. 4.3.2). Product separation from unreacted enelactone **20** by gravity column chromatography was difficult due to the overlapping nature of spots on TLC. KH/t-BuOOH developed by Still[14] and alkyl lithiums/t-BuOOH developed by Cohn et al[17] were not tried because of the hazardous nature of the reagents. Yamamoto's reagent[15] (Et_2Zn/O_2)

was also not attempted because of its high chemoselective nature for enones only.

The above unfortunate failures coupled with the literature reports[1-6] revealing the importance of oxiranes of electron deficient alkenes provided us the necessary impetus to study other easily adaptable reagents. We focussed on the use of t-BuOOH as the oxidant in conjunction with a base.

Part 4.2.1 t-BuOOH and KF-impregnated Al_2O_3

We, first, contemplated to use reagents supported on inorganic solids because they offer advantages in

(a) simple workup and products purification,

(b) enhanced or reduced reactivity of functional groups, and

(c) offering selectivity that may be different from that in solution.

Ando et al[19] adsorbed several first group metal fluorides on alumina and compared their activity in promting alkylation of phenols and alcohols. Although $CsF-Al_2O_3$ was discovered to be the most effective, $KF-Al_2O_3$ was preferred for its non-hydroscopic nature and its relatively much lower cost. Optimization of reagent preparation and elucidation of the active species were investigated[20,21]. This led to much enhanced research activity and $KF-Al_2O_3$ witnessed larger usage in (a) O-alkylation of phenols and alcohols;[19] (b) β-elimination[22], (c) Michael addition[20b], (d) condensation (Aldol[22], Darzens[22] and Knoevenagel[23]) reactions. We became interested in the $KF-Al_2O_3$ reagent and reasoned it suitable as a base in the epoxidation of electron-deficient alkenes with anhydrous t-BuOOH.

The enelactone **20** was allowed to react with anhydrous t-BuOOH in acetonitrile at room temperature. After 20h, only the starting material **20** was recovered intact. Undeterred by this failure, we wished to test this reagent with other systems. True to our expectations, a range of olefins reacted smoothly. The examples are collected in the Table. Following observations are noteworthy:

(a) acyclic enones such as chalcone **1** and dibenzalacetone **4** reacted extremely rapid to provide nearly quantitative yields of the corresponding epoxy products.

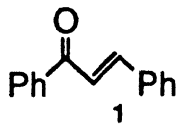
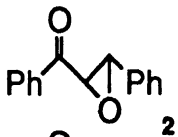
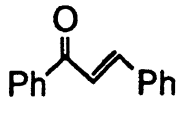
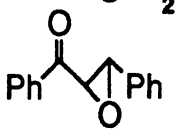
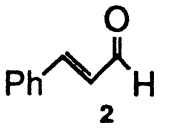
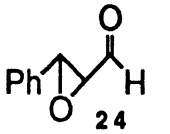
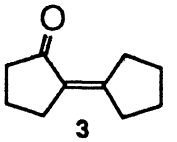
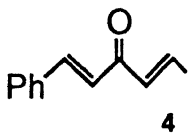
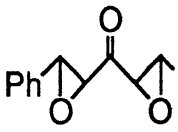
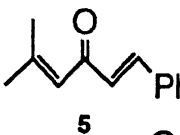
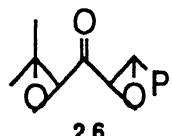
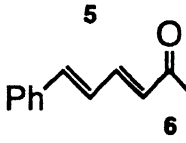
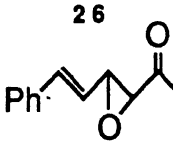
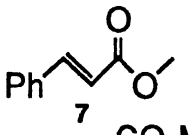
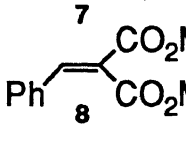
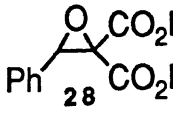
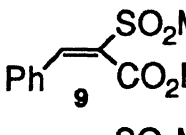
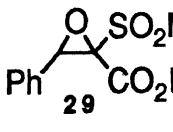
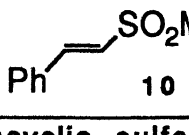
(b) interestingly, the monoepoxide from 5-methyl-1-phenyl-1,4--hexadien-3-one **5** (entry 5) reacts faster than the starting dienone itself. In an experiment in which the dienone was reacted with 1.2 mol equiv. of anhydrous t-BuOOH and 1.5 mol equiv. of KF-Al_2O_3, the products mixture comprised of a 1:1 mixture of the starting dienone and its bisepoxy derivative. The above ratio was assessed from the integrals of characteristic ^1H NMR signals.

(c) the dienone **6** (entry 6) reacted, although slow but with complete regioselection, to furnish only the α,β-epoxy derivative. It is important to note here that a reaction with alkaline H_2O_2 in MeOH for 12h was ineffective and returned only the starting material,

(d) the oxidation of cyclopentenone derivative (entry 19) is quantitative,

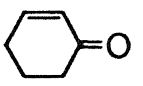
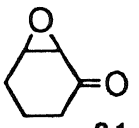
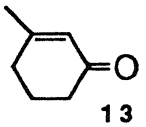
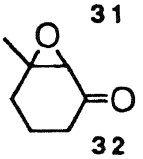
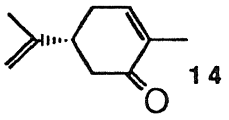
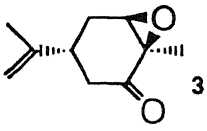
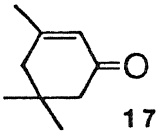
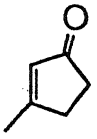
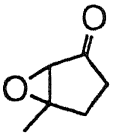
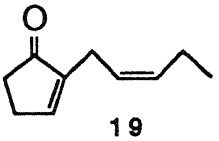
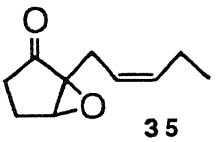
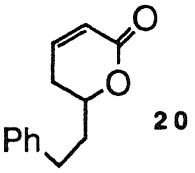
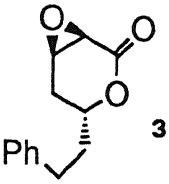
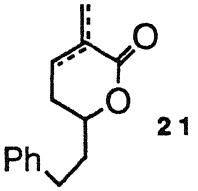
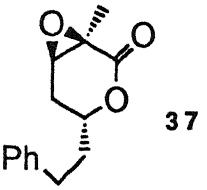
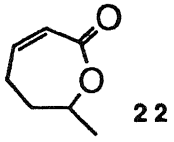
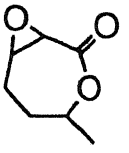
(e) reaction with acyclic α,β-unsaturated ester (entry 7) and unsaturated sulfones (entry 10) fails, but with doubly activated esters such as **8** and sulfone such as **9** (entries 8

Table

entry	substrate	product	time(h); Yield (%)[a] t-BuOOH KF-Al_2O_3	time(h); Yield (%)[a] t-BuOOH DBU
	acyclic enones			
1.	 1	 23	$\frac{1}{6}$; 100	10; 100
1a.				28; 100[b]
2.	 2	 24	5; 75[c]	10; 70[c]
3.	 3	no reaction	20; --	20; --
	acyclic dienones			
4.	 4	 25	$\frac{1}{6}$; 100[d]	10; 100[d]
5.	 5	 26	12; 87[d]	10; 80[d]
6.	 6	 27	56; 45[e]	96; 35[e]
	acyclic unsaturated esters and sulfones			
7.	 7	no reaction	15; --	15; --
8.	 8	 28	20; 35[f]	2; 100
9.	 9	 29	20; 34	$\frac{1}{2}$; 100
10.	 10	no reaction	32; --	32; --
	acyclic sulfonylimines			
11.	p $MeC_6H_4SO_2N{=}CHPh$ 11	p-$MeC_6H_4SO_2NHCOPh$ 30	4; decomp[n]	2; 95

---Table continued on next page

Table

entry	substrate	product	time(h); Yield (%)[a] t-BuOOH KF-Al_2O_3	time(h); Yield (%)[a] t-BuOOH DBU
	cyclohexenones			
12.	 12	 31	1; 85	10; 92
13.	 13	 32	20; 40	24; 65
14.	 14	 33	10; 85	12; 90
15.	Testosterone 15	no reaction	20; --	20; --
16.	Testosterone acetate 16	no reaction	20; --	20; --
17.	 17	no reaction	20; --	20; --
	cyclopentenones			
18.	 18	 34	20; 65[f]	24; 75[f]
19.	 19	 35	30; 100	30; 100
	Cyclic unsaturated ester			
20.	 20	 36	20; --	12; 75
21.	 21	 37	--; --	18; 35[g]
22.	 22	 38	--; --	27; 20

--Table continued on next page

[a]yields given are the isolated yields, unless indicated otherwise.

[b]this reaction was performed with 10mol% DBU wrt the substrate and 2 equiv of t-BuOOH.

[c]this reaction was nonstereospecific as a mixture of both *cis* and *trans* oxiranes were obtained

[d]mix of *cis* and *trans* oxiranes were obtained.

[e]from a very clean reaction, the conversion to the product was 45% ($KF-Al_2O_3$) and 35% (DBU), respectively (^1H nmr).

[f]the extent of conversion was computed from ^1H nmr spectral signals.

[g]the ratio of the *endo* lactenone and the *endo* oxirane was 3:2 (^1H nmr).

and 9), the reaction succeeds to afford the respective epoxides and

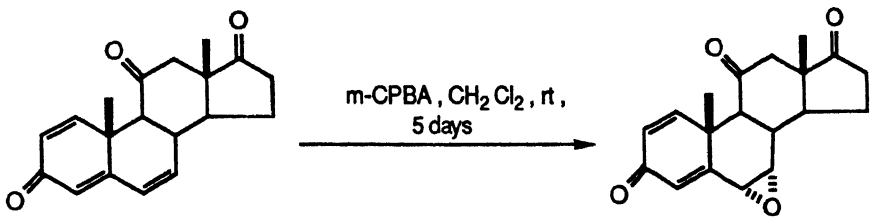
(f) whereas 2-cyclohexenone **12** reacted completely in 1h, 3-methyl-2-cyclohexenone **13** was much slow to offer only 40% conversion even after 20h; raising, therefore, the possibility of regioselective oxidations.

2-Cyclopentylidenecyclopentanone **3**, testosterone **15**, testosterone acetate **16**, isophorone **17**, α,β-unsaturated sulfone **10** and cyclic and acyclic α,β-unsaturated esters did not react and, in each case the substrate was recovered intact. These failures are due, probably, to the steric interference offered by the angular methyls in the steroid series, the axial methyl in isophorone, and low Michael acceptibility in α,β-unsaturated sulfone, cyclic and acyclic α, β-unsaturated esters. Failure of 2-cyclopentylidenecyclopentanone to react under conditions in which 3-methyl-2-cyclohexenone **13** and 5-methyl-1-phenyl-1,4-hexadien-3-one **5** reacted well is indeed surprising.

The success in achieving the oxidation of the 2-cyclopentenone derivatives is remarkable. These materials are known to be highly prone to base catalysed self condensation of aldol type. No aldol products were noticed in the present study.

Although the testosterone-acetate was unreceptive to oxidation by t-BuOOH/KF-Al_2O_3, the survival of the acetoxy function in the recovered material could be taken as a testimony to the mildness of this reagent system over the existing methods. Further, functional groups that are labile to aqueous bases stand to retain their identity under the present conditions.

Burdett et al[24] reported that the dienones **40** with extended conjugation undergoes peracid epoxidation stereo- and



40 **41**

regioselectively at the γ,δ-double bond. The mCPBA oxidation, therefore, is complementary to our KF-Al_2O_3/t-BuOOH method. The obvious reason is, ofcourse, the switchover in mechanism from nucleophilic to electrophilic nature of the oxidant.

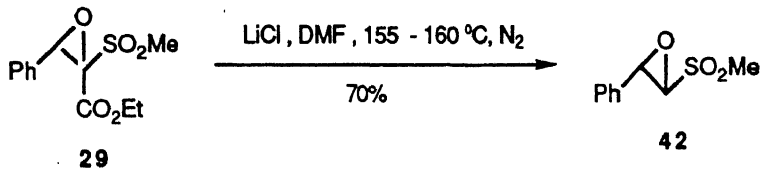
Whereas the t-BuOOH/KF-Al_2O_3 system furnished, on reaction with chalcone **1** and dienone **6**, only the *trans* oxiranes,other acyclic materials such as dibenzalacetone **4** and 5-methyl-1-phenyl-1,4-hexadien-3-one **5** gave a mixture of *trans* and *cis* oxides as revealed by their ^{1}H NMR spectra. These results show that the present reaction is not stereospecific with the latter systems. The reason for such a discrepancy in stereospecficity is not clear. The present system is also fruitful with aldehydes such as cinnamaldehyde (entry 2) where, again, an inseparable mixture of *cis* and *trans* oxides is received (^{1}H NMR spectrum). This result is at variance from that achieved with alkaline H_2O_2[9].

The oxidation of α,β-unsaturated sulfones is an important reaction. A limited number of methods are available[25,26]. Phenyl β-phenylvinyl sulfones under Weitz-Scheffer conditions undergo

stereospecific epoxidation to give the *trans* epoxides from both the *cis* and the *trans* alkenes[27]. Potassium t-butylhydroperoxide is not stereospecific and transforms *cis* phenyl β-phenylvinyl sulfone into a *cis/trans* (= 2/3) mixture of corresponding oxiranes. The alkyllithiums/t-BuOOH method of Cohn et al[17] provides an excellent stereospecific solution; the yields of the requisite oxiranes are very high and, moreover, the initial stereo-integrity of the olefinic bond is retained in the product epoxide.

We looked at the possibility of entry to epoxy sulfones by either direct oxidation of methyl vinyl sulfone **10** or performing dealkyldecarboxylation of the epoxy material **29** (Scheme 4.2.2).

Scheme 4.2.2



29 **42**

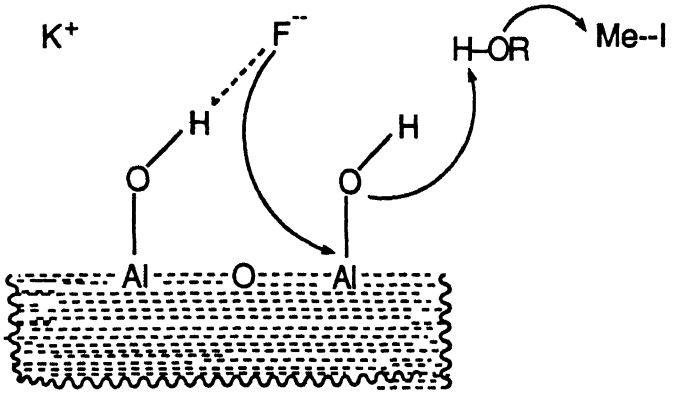
The direct oxidation proved futile. The further activated sulfone **9** reacted, though slowly, to afford the requisite oxirane. This on reaction with LiCl/DMF at 155-160 ^{o}C under N_2 gave the desired epoxy sulfone **42**. The structure of **42** was assigned based on the spectral data and elemental analysis.

In a bid to obtain the Davis reagent[8] by epoxidation of N-(p-toluenesulfonyl)benzylimine **11** with our newly developedoxidation system, only decomposition of the starting

imine **11** top-toluenesulfonamide and benzaldehyde was noticed.

Ando et al have reported[20a] that KF-Al_2O_3 owes its efficient and versatile reactivity as a heterogeneous base for organic synthesis to at least three possible mechanisms: (a) dispersion and increased surface area of KF giving co-ordinately unsaturated F^-, (b) liberation of strong base during preparation, and (c) the co-operative action of F^- and the hydrated alumina surface as shown in Scheme 4.2.3 for the alkylation of alcohols.

Scheme 4.2.3



In order to reflect on the mechanism of oxidation, t-BuOOH was replaced by MeI in an experiment with chalcone. Chalcone was recovered unchanged. Absence of PhCH(F)CH(Me)COPh negates the halohydrin pathway that may be conceived arising from conjugate addition of fluoride ion and quench of the enolate with t-BuOOH. We believe that a mechanism similar to that shown in Scheme 4.2.3 is operative in our case also.

4.2.2 t-BuOOH and 1,8-Diazabicyclo[5,4,0]undec-7-ene (DBU)

Our newly developed oxidation system t-BuOOH/KF-Al_2O_3][28]

has resulted in the preparation of oxiranes from a wide variety of electron deficient olefins but failed to produce the aimed epoxide **36** from the enelactone **20**. The inertness of enelactone **20** in oxidation with t-BuOOH/KF-Al_2O_3 may be conceived due to

(a) poor Michael acceptibility of cyclic α,β-unsaturated ester **20**, and

(b) complexed nature of t-$BuOO^-$ with KF-Al_2O_3.

We looked at the complexed aspect and envisioned to replace KF-Al_2O_3 by non-nucleophilic tertiary amines. This consideration was translated into reality when we discovered DBU promote the much desired epoxidation by anhydrous t-BuOOH in dichloroethane. The reaction proceeded stereoselectively to furnish, after chromatographic purification, the product oxirane **36** in >75% yield. The characterization and disasteroselectivity effects have already been discussed in the previous chapter (cf 3.2). Other bases that we examined were triethylamine, diisopropylethylamine (Hünig base) and 1,4-diazabicyclo[2.2.2]octane (DABCO), and were found ineffective.

Encouraged from the above findings we set to explore the scope and reacted other substrates. The results are collected in the Table alongside the results from KF-Al_2O_3 for better comparison. Reaction on a mixture of *endo* and *exo* δ-lactenones **21** (entry 21) furnished a mixture consisting of *endo* lactenone **42** and the oxirane **37** derived from it (Scheme 4.2.4). The formation of **37** has been confirmed by spectral data and elemental analysis (cf expt.4.3.28). Apparently, the *exo* lactenone isomerized# to the

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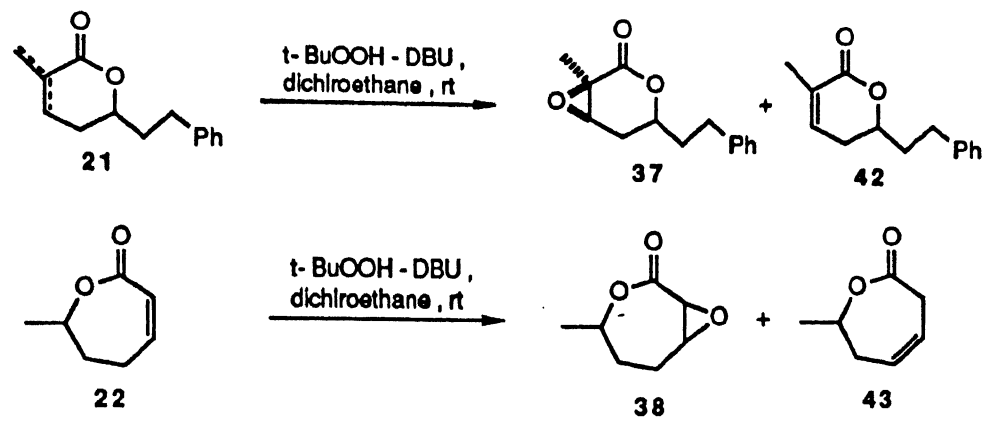
This concept of deconjugative isomerization and its utility to architect the synthons of natural products will be dealt with in Chapter 5.

endo counterpart which underwent slow oxidation to the product under similar conditions. The 7-membered conjugated enelactone **22**

Scheme 4.2.4



furnished, other than the unreacted starting material, the deconjugated material **43**, and possibly the oxirane **38**. The R_f values of the materials **22** and **38** are very similar, making their separation difficult. From IR (1720 and 1700 cm^{-1}, strong bands of almost equal intensity) and ^1H NMR spectra (an additional doublet for methyl at ppm 1.1, J = 6 Hz and an additional multiplet for $CH_3C\underline{H}O$- adjacent that for $CH_3C\underline{H}O$- in the enelactone **22**) of this mixture, the presence and the hence the formation of **38** was discerned.

In an experiment wherein the lactenone **22** was reacted with mCPBA in dichloroethane at reflux, the respective epoxide was isolated in 22% yields; the remainder has curiously isomerized to the deconjugated species **43**. The oxirane so obtained, displays ^1H signals wherein the chemical shifts for $CH_3C\underline{H}O$- (ppm 5.3) and the oxirane protons (ppm 3.75, d, 1H, J = 3.5 Hz and ppm

3.5, m, 1H) appear downfield compared to those of **38**. The epoxide obtained from mCPBA oxidation is, therefore, epimeric to **38**. Though the individual stereo-identity was not established, the material obtained from peracid oxidation is likely to be the *trans* oxirane. The epoxy oxygen exerts anisotropic effect on the $CH_3C\underline{H}O$- proton, pushing the latter downfield on NMR scale.

Recognising the potency of t-BuOOH/DBU reagent system, we wished to explore its versatality and, therefore, reacted electrophilic alkenes of differing substitution pattern. In comparison to KF-Al_2O_3 based reagent, certain observations are noteworthy:

(a) enones (**1**, **4**, **6** and **12**) reacted much slower.

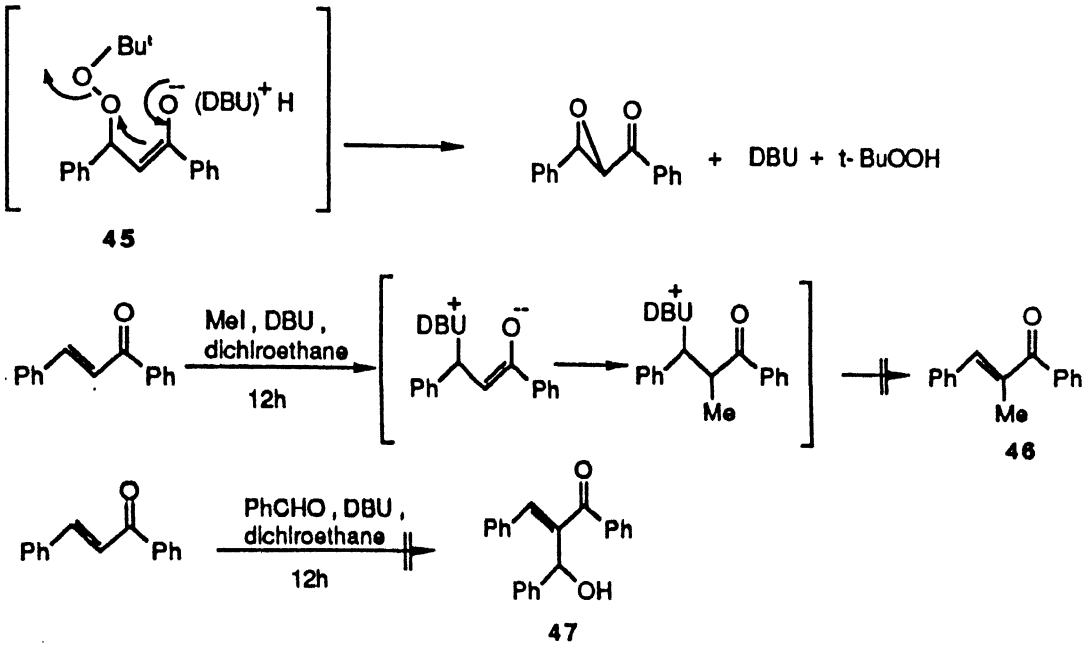
(b) doubly activated alkenes such as **8** and **9** reacted at a much faster rate.

The use of 70% t-BuOOH in place of anhydrous t-BuOOH in reaction of chalcone gave an intractable mixture of side products. Other observations noticed for t-BuOOH/KF-Al_2O_3 reagent system are valid for this reagent system also.

Finally, the Davis reagent[8] is obtained by oxidation of N-(p-toluenesulfonyl)imine **11** with mCPBA using lipophilic phase-transfer catalyst such as benzyltriethylammonium chloride[29]. We considered applying the present methodology. The reaction of imine **11** with DBU-based reagent offered the rearranged product **30** (entry 11) in near quantitative yields. Compound **30** was assigned structure based on spectral data and elemental analysis (cf. expt. 4.3.20). Obviously, the requisite epoxide is first formed which then quickly rearranges, under the reaction conditions, to the observed product.

1,4-Addition of t-butylperoxy anion followed by attack of resultant enolate on the *per* oxygen accounts for product(s)

Scheme 4.2.5



formation. In an experiment in which methyl iodide was substituted for t-BuOOH and chalcone used as the reacting substrate, compound **46** (Scheme 4.2.5) was not received. Likewise, in another experiment in which t-BuOOH was replaced by benzaldehyde, compound **47** was not isolated. In each case, chalcone was recovered intact. These observation argue against a reaction pathway which may be conceived to initiate by conjugate addition of DBU following

(a) attack of the resultant enolate on the *per* oxygen of t-BuOOH giving an α-hydroxy intermediate which subsequently

(b) undergoes an intramolecular ring closure to furnish the

used, stands for diethyl ether. The organic extracts were dried over anhydrous Na_2SO_4 and solvents were removed under reduced pressure on rotovap. Commonly used abbreviations are used throughout. Solvents used in this study were dried as per established procedures.

Details of the instruments used are the same as described in experimental section of Chapter 2, ^1H Chemical shifts are reported in parts per million (ppm) from tetramethylsilane. Neutral alumina (Batch No. S/0193/892/301211, Brockmann grade 1, for column chromatography) was procured from S.d. Fine Chemicals Ltd., Bombay, India. KF was dried *in vacuo* at 110 ^oC for 6h using Abderhalden drying apparatus. DBU (Fluka) was distilled under reduced pressure and used as such throughout the study.

4.3.1 Reaction of enelactone 20 with $H_2O_2/NaHCO_3$ in MeOH[10]

To a solution of enelactone **20** (0.065 g, 0.321 mmol) in MeOH (11 ml) was added, at 0 ^oC, 0.5 M aq $NaHCO_3$ solution (2 ml, 1.0 mmol) followed by 30% aq H_2O_2 (226 μl, 2.0 mmol) and the resultant allowed to come to rt. The solution became turbid and started becoming clear with the passage of time. After stirring at rt for 16h the reaction mix was diluted with $CHCl_3$ (44 ml) and H_2O (44 ml). The layers were separated and aq phase extracted with $CHCl_3$ (2 x 15 ml). The combined organic layers was washed with saturated aq Na_2SO_3 (3 x 25 ml), H_2O (1 x 20 ml) and brine (1 x 25 ml). Drying, solvents removal gave a residue which was chromatographed to afford ***methyl 2,3-epoxy-5-hydroxy-7-phenylheptanoate* 39** (0.016 g, 20%) and the starting enelactone **20** (0.035 g, 54%).

^{1}H NMR (60 MHz) : ppm 7.0 (s, 5H, Ar-H), 3.6 (s, 3H, -(O)COCH$_3$), 3.4-3.0 (m, 2H, -CH(OH), oxirane-H, α to carbonyl), 2.8-2.2 (m, 4H, OH, oxirane-H, β to carbonyl, PhCH$_2$-), 1.9-1.5 (m, 4H, 2xCH$_2$).

IR (neat), ν_{max} : 3480 (hydroxyl), 1730 (carbonyl), 1270, 900 and 750 cm^{-1}.

Mass (m/z) : 250 (M^+).

Analysis calcd.for $C_{14}H_{18}O_4$: C, 67.2, H, 7.2;
Found : C, 67.41, H, 7.44%.

4.3.2 Reaction of enelactone 20 with mCPBA[11]

A solution of enelactone (0.054 g, 0.26 mmol) and mCPBA (0.2 g of 45% mCPBA, 0.52 mmol) in dichloroethane (2 ml) was refluxed for 6h. After cooling to rt the reaction mix was diluted with $CHCl_3$ (5 ml).To this, was added saturated aq Na_2SO_3 solution (2 ml) and stirring continued for another 30 min. The reaction mix was partitioned between $CHCl_3$ (15 ml) and H_2O (5 ml). The layers were separated and aq phase extracted with $CHCl_3$ (2 x 5 ml). The combined organic extracts was washed with 10% aq $NaHCO_3$ (2 x 5 ml), H_2O (1 x 5 ml) and brine (1 x 7 ml). Drying, evaporation of solvents and column chromatography of the residue furnished viscous material (0.037 g, 66%) which was found to be a 6:4 mixture (^{1}H NMR) of desired oxirane **36** and starting enelactone **20**, nevertheless, only single spot appeared on the TLC (15% Ethyl acetate/Pet.ether as eluant, double run). **36** displayed ^{1}H NMR and IR spectra resembling that of compound **9** of Chapter 3 (cf expt. 3.3.7).

4.3.3 Preparation of anhydrous t-BuOOH following the Sharpless and Verhoeven's procedure[30]

(4 ml, 2.88 mmol) of 70% t-BuOOH in dichloroethane and 6.8ml dichloroethane were combined in 25 ml separatory funnel andswirled for about one min and allowed unperturbed for 15 min. Two layers formed and lower layer was drained into a one necked, round-bottomed flask through a small pad of Na_2SO_4. Thisdichloroethane solution contained 2.35 mmol/ml of anhydroust-BuOOH and stored in the refrigerator.

4.3.4 Preparation of KF-impregnated Al_2O_3 adopting the Ando et al's procedure[19]

Anhydrous KF (58 g, 1 mol) was dissolved in distilled H_2O (100 ml) and mixed with neutral alumina (100 g). The H_2O was removed at 45-50 ^oC on rotovap under reduced pressure. This impregnated alumina was further dried at 75 ^oC for 30h in a vacuum drying oven. The free flowing material thus obtained contained 6.33 mmol KF/g and was stored in a plastic bottle at rt and used throughout this study.

4.3.5 General method for oxidation with t-BuOOH and KF-Al_2O_3[28]

To a stirred suspension of KF-Al_2O_3 (0.475 g, 3 mmol of KF) in dry acetonitrile (6 ml), at 5 ^oC, was added, dropwise, 2.35 M dichloroethane solution of anhydrous t-BuOOH (1.7 ml, 4 mmol of t-BuOOH). After 5 min the reacting olefin (2 mmol) solution in dry acetonitrile (2 ml) was added. The resultant was stirred at rt and monitored for completion. Simple filteration and evaporation of volatiles under reduced pressure furnished the

product(s) which, if necessary, could be filtered through a silica gel column.

4.3.6 General procedure for the oxidation with t-BuOOH and DBU

A dichloroethane solution (2.0 ml) of the substrate (1 mmol) was added to a solution of DBU (0.182 g, 1.2 mmol) and anhydrous t-BUOOH (850 μl of a 2.35 M solution in dichloroethane, 2.0 mmol) in dry dichloroethane (2.0 ml) at 5 ^{o}C. The resultant mix was stirred at rt and monitored for completion. The volatiles were removed under reduced pressure and the residue filtered rapidly through a small silica gel column to furnish the product.

4.3.7 *Trans* 2,3-epoxy-1,3-diphenylpropane-1-one [*Trans* chalcone epoxide] 23

m p : 86 - 87 ^{o}C (lit[31]. 89 ^{o}C)

^{1}H NMR (90 MHz) : ppm 8.3-7.8 (m, 2H, Ar-H, *meta* to carbonyl), 7.8-7.1 (m, 8H, Ar-H), 4.3 (d, 1H, J = 2 Hz, oxirane-H, β to carbonyl), 4.1 (d, 1H, J = 2 Hz, oxirane-H, α to carbonyl).

IR (KBr), ν_{max} : 1680 (C=O), 1445, 1410, 1235, 880 and 750 cm^{-1}.

4.3.8 *Trans* 2,3-epoxy cinnamaldehyde 24

^{1}H NMR (60 MHz) : ppm 9.3 (d,1H, J = 6 Hz, -HC=O), 7.4 (s, 5H, Ar-H), 4.1 (d, 1H, J = 2Hz, oxirane-H, β to carbonyl), 3.4-3.2 (dd, 1H, J = 6 & 2 Hz, oxirane-H, α to carbonyl).

***Cis* 2,3-epoxy cinnamaldehyde 24**

^{1}H NMR (60 MHz) : ppm 9.2 (d, 1H, J = 6 Hz, -HC=O), 7.3(s, 5H,

ArH), 4.4 (d, 1H, J = 4.5 Hz, oxirane-H, β to carbonyl), 3.6-3.3 (d, 1H, J = 6 and 4.5 Hz, oxirane-H, α to carbonyl).

IR spectrum of 24 [Cis/trans]

(neat), ν_{max} : 1715 (C=0), 1240, 890 and 770 cm^{-1}.

Mass spectrum of 24 (m/z) : 149 ($M^+ + 1$), 148 (M^+).

4.3.9 Dibenzalacetone epoxide 25

^1H NMR (60 MHz) : ppm 7.4 (s, 10H, ArH), 4.1 (m, 2H, 2x oxirane-H, β to carbonyl), 3.6 (m, 2H, 2x oxirane-H, α to carbonyl).

IR (neat), ν_{max} : 1710 (C=0), 1220, 880 and 750 cm^{-1}.

Analysis calcd.for $C_{17}H_{14}O_3$: C, 76.69, H, 5.26;
Found : C, 76.58, H, 5.13%.

4.3.10 Preparation of 5-methyl-1-phenyl-1,4-hexadien-3-one 5

To a solution of mesityl oxide (0.98 g, 10.0 mmol) and benzaldehyde (1.06 g, 10.0 mmol) in ethanol (25 ml) was added a solution of NaOH (0.80 g, 20.0 mmol) in a 2:1 mix of EtOH and H_2O (15 ml) at 0^oC under N_2. The reaction solution was allowed to come to rt and the stirring continued. After 4h, most of the EtOH was removed on rolovap, the residue diluted with H_2O (20 ml), and extracted with ether (3 x 25 ml). The combined extract was washed with brine (1 x 20 ml), dried, and concentrated. The residue was chromatographed to furnish the desired product **5** (1.02 g, 55%).

^1H NMR (60 MHz) : ppm 7.8 (d, 1H, J = 16 Hz, PhCH=CH), 7.7-7.3 (m, 5H, Ar-H), 6.8 (d, 1H, J = 16 Hz, PhCH=CH-), 6.4 (m, 1H, -CH=CMe_2), 2.3 (s, 3H, -CH_3), 2.0 (s, 3H, -CH_3)

IR (neat), ν_{max} : 1700 (C=0), 1665, 1620, 1590, 1570, 1445 and 1115 cm^{-1}.

Mass (m/z) : 186 (M^+).

4.3.11 1,2;4,5-diepoxy-5-methyl-1-phenylhexan-3-one 26

^{1}H NMR (80 MHz) : ppm 7.5 (bs, 5H, Ar-H), 4.2-3.6 [4.19(d), 4.0(d), 3.84(d), 3.75(d), 3.70(s), 3.53(s), 3.53(s), 3H, 3 x oxirane-H)], 1.50-1.34 [1.50(s), 1.40(s), 1.34(s), 6H, 2 x $-CH_3$).

IR (neat), ν_{max} : 1705 (C=0), 1665, 1615, 1440, 1235, 1110, 870 and 750 cm^{-1}.

Mass (m/z) : 218 (M^+).

Analysis calcd.for $C_{13}H_{14}O_3$: C, 71.56, H, 6.42;
Found : C, 71.63, H, 6.51%.

4.3.12 Preparation of 6-phenyl-3,5-hexadien-2-one 6

To a well stirred slurry of KF-Al_2O_3 (1.42 g, 9.0 mmol of KF) in dry acetonitrile (10 ml) at 5 ^oC was, added, a mixed solution of cinnamaldehyde (0.792 g, 6.0 mmol) and acetone (1.16 g, 20.0 mmol) in dry acetonitrile (10 ml) dropwise over a period of 30 min. The reaction mix was allowed to come to rt when the solution turned dark orange in color from the initial yellow. After 2.5 h, KF-Al_2O_3 was removed by filteration, the filterate freed of solvent, and residue chromatographed to furnish the orange colored viscous liquid **6** (0.30 g, 30%).

^{1}H NMR (60 MHz) : ppm 7.7-7.1 (m, 6H, ArH, -(O)CCH=CH-), 7.1-6.6 (m, 2H, -(O)CCH=CH-CH=CH-), 6.3-6.0 (dd, 1H, J = 15 and 2 Hz, -(O)CCH=CH-CH=CH-), 2.2 (s,

3H, -(O)CC$\underline{H}_3$).

IR (neat), ν_{max} : 1650 (C=O), 1610, 1350 and 1250 cm^{-1}.

Mass (m/z) : 172 (M^+).

Analysis calcd.for $C_{12}H_{12}O$: C, 83.72, H, 6.98;

Found : C, 83.58, H, 6.81%.

4.3.13 3,4-Epoxy-6-phenyl-5-hexen-2-one 27

This epoxide was inseparable from the parent dienone by gravity column chromatography. The ^1H NMR spectrum (60 MHz) of the mixture consists of the following signals that are characteristics of *trans* epoxide:

ppm 3.6 (dd, 1H, J = 7 & 2 Hz, oxirane-$\underline{H}$, β to carbonyl), 3.3 (d, 1H, J = 2Hz, oxirane-$\underline{H}$, α to carbonyl), 2.0 (s, 3H, -(O)CC$\underline{H}_3$).

IR (neat), ν_{max} : 1705 cm^{-1}.

Mass (m/z) : 188 (M^+).

4.3.14 Preparation of benzylidene dimethyl malonate 8

Dimethylmalonate (1.32 g, 10.0 mmol), benzaldehyde (1.27g, 12.0 mmol) and piperidine (0.086 g, 1.0 mmol) were taken in benzene (50 ml) and refluxed under N_2 with azeotropic removal of H_2O formed during the reaction using Dean-Stark apparatus. After 9h the reaction mix is cooled to rt and poured into a well stirred cold 5% aq HCl (10 ml) covered with ether (20 ml). The layers were separated and the aq phase extracted with ether (2 x 15 ml). The combined ether extracts was washed successively with H_2O (1 x 20 ml) and brine (1 x 20 ml). Drying, filteration and solvent removal furnished a residue which was chromatographed to isolate the desired product **8** (2.1 g, 95%).

^{1}H NMR (60 MHz) : ppm 7.9 (s, 1H, PhC$\underline{H}$=C<), 7.5(s, 5H, Ar-$\underline{H}$), 3.9 (s, 3H, -COOC$\underline{H}_3$), 3.85 (s, 3H, -COOC$\underline{H}_3$).

IR (neat), ν_{max} : 1720 (br, C=0), 1620, 1430, 1260 and 1050 cm^{-1}.

Mass (m/z) : 220 (M^+).

4.3.15 Methyl 2-Carbomethoxy-2,3-epoxy-3-phenylpropionate 28

^{1}H NMR (60 MHz, $CDCl_3$) : ppm 7.3 (s, 5H, Ar$\underline{H}$), 4.5 (s, 1H, oxirane-$\underline{H}$), 3.9 (s, 3H, -$CO_2C\underline{H}_3$), 3.5 (s, (3H, $CO_2C\underline{H}_3$).

IR (neat), ν_{max} : 1745 (br, C=0), 1630, 1260, 1120 and 790 cm^{-1}.

Analysis calcd.for $C_{12}H_{12}O_5$: C, 61.02, H, 5.08;
Found : C, 61.11, H, 5.00%.

4.3.16 Preparation of Ethyl β-methylsulfonylcinnamate 9

Compound **9** was prepared by Knoevenagel condensation between ethyl methylsulfonyl acetate and benzaldehyde as per the procedure of Happer and Steenson[32]; 97% yield.

m p : 54 - 55 °C (lit[32]. 53 - 55 °C).

^{1}H NMR (60 MHz, $CDCl_3$) : ppm 7.7 (s, 1H, PhC$\underline{H}$=C<), 7.5 (s, 5H, Ar-$\underline{H}$), 4.3 (q, 2H, J = 7 Hz, COOC$\underline{H}_2$CH$_3$), 3.1 (s, 3H, -$SO_2C\underline{H}_3$), 1.3 (t, 1H, J = 7 Hz, -$CH_2C\underline{H}_3$).

IR (neat), ν_{max} : 1715 (C=0), 1615, 1310, 1220 and 1140 cm^{-1}.

Ethylmethylsulfonyl acetate was prepared by reacting ethylacetoacetate with sodium ethoxide and methylsulfonyl chloride following the procedure of Huppatz[33].

4.3.17 Preparation of methyl styryl sulfone 10

The above compound **9** was subjected to dealkyldecarboxylation as per the procedure of Happer and Steenson[32] to receive the product **10** in 70% yield.

m p : 78 - 79 ^{o}C (lit[32]. 77 - 78 ^{o}C).

^{1}H NMR (60 MHz, $CDCl_3$) : ppm 7.7 (d, 1H, J = 16 Hz, PhC<u>H</u>=CH<), 7.5 (s, 5H, Ar-<u>H</u>), 7.0 (d, 1H, J = 16 Hz, PhCH=C<u>H</u>-), 3.0 (s, 3H, $-SO_2C\underline{H}_3$).

IR (KBr), ν_{max} : 1610, 1565, 1485, 1140, 1130 and 960 cm^{-1}.

4.3.18 Ethyl 2-methylsulfonyl-2,3-epoxy-3-phenylpropionate 29

^{1}H NMR (60 MHz, $CDCl_3$) : ppm 7.8 (s, 5H, Ar-<u>H</u>), 4.8 (s, 1H, PhC<u>H</u>-), 4.2 (q, 2H, J = 7 Hz, $-OC\underline{H}_2CH_3$), 3.2 (s, 3H, $-SO_2C\underline{H}_3$), 1.0 (t, 3H, J = 7Hz, $-OCH_2C\underline{H}_3$).

IR (neat), ν_{max} : 1730 (C=0) and 1320 cm^{-1}.

Mass (m/z) : 270 (M^+).

Analysis calcd.for $C_{12}H_{14}O_5S$: C, 53.33, H, 5.18, S, 11.85;
Found : C, 53.45, H, 5.26, S, 11.76%.

4.3.19 Epoxystyrylmethyl sulfone 42

The epoxide **29** (0.181 g, 0.67 mmol) and LiCl (0.57 g, 1.34 mmol) were cooked in dry DMF (6.0 ml) at 155 - 160 ^{o}C for 35 min. The reaction was allowed to come to rt and poured into cold H_2O (25 ml). This was extracted with ether (3 x 30 ml) and the combined extracts washed with cold H_2O (2 x 20 ml) and brine (1 x 25 ml). Drying and concentration furnished the residue that was

chromatographed to afford the desired product **42** (0.80 g, 70%).

^{1}H NMR (60 MHz, $CDCl_3$) : ppm 7.6 (s, 5H, Ar-H), 4.4 (s, 2H, oxirane-H), 2.8 (s, 3H, $-SO_2CH_3$).

IR (neat), ν_{max} : 1300 and 1115 cm^{-1}.

Analysis calcd.for $C_9H_{10}O_3S$: C, 54.54, H, 5.05, S, 16.16;

Found : C, 54.40, H, 4.90, S, 16.10%.

4.3.20 N-(p-Toluenesulfonyl)benzamide 30

^{1}H NMR (60 MHz, $CDCl_3$) : ppm 8.1-7.6 (m, 4H, Ar-H), 7.6-7.0 (m, 5H, Ar-H), 5.6-5.0 (bs, 1H, -NH-), 2.4 (s, 3H, $-CH_3$).

IR (KBr), ν_{max} : 3300, 1700, 1600 and 1180 cm^{-1}.

Mass (m/z) : 275 (M^+).

Analysis calcd. for $C_{14}H_{13}NO_3S$: C, 61.09, H, 4.72, N, 5.09, S, 11.63;

Found : C, 60.81, H, 4.50, N, 5.21, S, 11.82%.

4.3.21 2,3-Epoxycyclohexanone 31

^{1}H NMR (60 MHz) : ppm 3.7 (m, 1H, oxirane-H, β to carbonyl), 3.2 (d, 1H, J = 4 Hz, oxirane-H, α to carbonyl), 2.9-1.4 (m, 6H, $3xCH_2$).

IR (neat), ν_{max} : 1700 (C=0), 1245, 870 and 810 cm^{-1}.

Mass (m/z) : 112 (M^+).

4.3.22 2,3-Epoxy-3-methylcyclohexanone 31

b p : 94 - 95 ^oC/12 mm

^{1}H NMR (60 MHz) : ppm 2.9 (s, 1H, oxirane-H, α to carbonyl),

2.3-1.5 (m, 6H, 3x$C\underline{H}_2$),1.43 (s, 3H, -$C\underline{H}_3$).

IR (neat), ν_{max} : 1700 and 860 cm^{-1}.

Mass (m/z) : 126 (M^+).

4.3.23 2,3-Epoxy-5-isopropenyl-2-methylcyclohexanone [R-(-)-carvone epoxide] 33

b p : 158 ^oC/7 mm (lit[34]. 160 ^oC/ 7 mm)

^1H NMR (60 MHz) : ppm 4.8 (m, 2H, >C=$C\underline{H}_2$), 3.4 (m, oxirane-$\underline{H}$, β to carbonyl), 3.0-1.5 (m, 5H, 2x$C\underline{H}_2$, 1x$C\underline{H}$), 1.8 (s, 3H, $CC\underline{H}_3$), 1.4 (s, 3H, -$C\underline{H}_3$).

IR (neat), ν_{max} : 1700, 1660, 1435, 1115 and 885 cm^{-1}.

Mass (m/z) : 166 (M^+).

4.3.24 2,3-Epoxy-3-methylcyclopentanone 34

^1H NMR (60 MHz) : ppm 3.0 (s, 1H, oxirane-$\underline{H}$, α to carbonyl), 2.5-1.9 (m, 4H, 2x$C\underline{H}_2$), 1.5 (s, 3H, -$C\underline{H}_3$).

IR (neat), ν_{max} : 1740 (C=0), 1270, 950 and 830 cm^{-1}.

Mass (m/z) : 126 (M^+).

4.3.25 2,3-Epoxy-2-(*cis/trans* 2-pentenyl)cyclopentanone 35

^1H NMR (60 MHz) : ppm 5.8-5.0 (m, 2H, -$\underline{H}$C=C$\underline{H}$-), 3.7 (s, 1H, oxirane-$\underline{H}$, β to carbonyl), 3.0-1.7 (m, 8H, 4x$C\underline{H}_2$), 1.0 (t, 3H, J = 7 Hz, -$CH_2C\underline{H}_3$).

IR (neat), ν_{max} : 1730 (C=0), 1050, 980 and 850 cm^{-1}.

Mass (m/z) : 167 (M^+ + 1), 166 (M^+).

4.3.26 3,4-Epoxy-6-(2-phenylethyl)tetrahydropyran-2-one 36

Spectral details and elemental analysis of oxirane **36** *have already been discerned in Chapter 3 (cf expt. 3.3.7).*

4.3.27 3-Methylidene-6-(2-phenylethyl)tetrahydropyran-2-one and 3,4-dehydro-3-methyl-6-(2-phenylethyl)tetrahydropyran-2-one 21

The preparation of a mixture of these two materials will be delineated in the experimental section of Chapter 5.

4.3.28 3,4-Epoxy-3-methyl-6-(2-phenylethyl)tetrahydropyran-2-one 37

^{1}H NMR (80 MHz) : ppm 7.2 (m, 5H, Ar-H), 4.5 (m, 1H, -(O)COCH-), 3.43 (d, 1H, J = 3 Hz, oxirane-H), 2.9-2.55 (m, 2H, $PhCH_2CH_2$-), 2.2-1.6 (m, 4H, $2xCH_2$), 1.56 (s, 3H, $-CH_3$).

IR (neat), ν_{max} : 1720 (C=0), 1160, 1000, 945 and 840 cm^{-1}.

Mass (m/z) : 233 ($M^+ + 1$), 232 (M^+).

Analysis calcd.for $C_{14}H_{16}O_3$: C, 72.41, H, 6.89;
Found : C, 72.12, H, 6.57%.

4.3.29 6,7-Dehydro-3-methyl-2-oxepanone 22

The preparation of compound **22** *from 2-methylcyclohexanone will be described in the experimental section of Chapter 5.*

4.3.30 *Trans* 6,7-epoxy-3-methyl-2-oxepanone 38

Following the procedure as described for expt. 4.3.2, enelactone **22** (0.02 g, 0.158 mmol) was subjected to oxidation with mCPBA (0.12 g of 45% mCPBA, 0.31 mmol) in refluxing dichloroethane (1.5 ml) for 4h to afford, after chromatography, 0.005 g (22%) of *trans* oxirane **38** and 0.01 g (50%) of deconjugated material **43**.

The spectral details of **43** *will be presented in experimental section of Chapter 5.*

^{1}H NMR of *trans* **43 (80 MHz)** : ppm 5.3 (m, 1H,-(O)COC<u>H</u>-), 3.7 (d, 1H, J = 4 Hz, oxirane-<u>H</u>, α to carbonyl), 3.43 (m, 1H, oxirane-<u>H</u>, β to carbonyl), 2.56-2.0 (m, 2H, 1XC<u>H</u>$_2$), 1.9-1.5 (m, 2H, 1xC<u>H</u>$_2$), 1.5 (d, 3H, J = 6 Hz, -C<u>H</u>$_3$).

IR spectrum of *trans* **43 (neat),** ν_{max} : 1710 (C=0), 1280, 1100, 1060 and 825 cm^{-1}.

Mass spectrum of *trans* **43 (m/z)** : 142 (M^+).

4.3.31 *Cis* **6,7-epoxy-3-methyl-2-oxepanone 38**

The enelactone **22** (0.02 g, 0.158 mmol) on submission to reaction conditions described in expt. 4.3.6 furnished, after chromatography, the deconjugated material (0.01 g, 50%) and 0.06 g of inseparable mix of starting material **22** and expected *cis* epoxide **38** (65% conversion as computed by integrals in ^{1}H NMR spectrum). The ^{1}H NMR spectrum (90 MHz) of mixture consists of following signals that are diagnostic of *cis* epoxide **38** :

ppm 4.8-4.1 (m, 1H, -OC<u>H</u>CH$_3$), 3.31-2.9 (m, 2H, oxirane-<u>H</u>), 1.37 (d, 3H, J = 6 Hz, -C<u>H</u>$_3$).

IR spectrum of mixture showed strong bands at 1720 (epoxy lactone) and 1700 cm^{-1} (enelactone) of almost equal intensity.

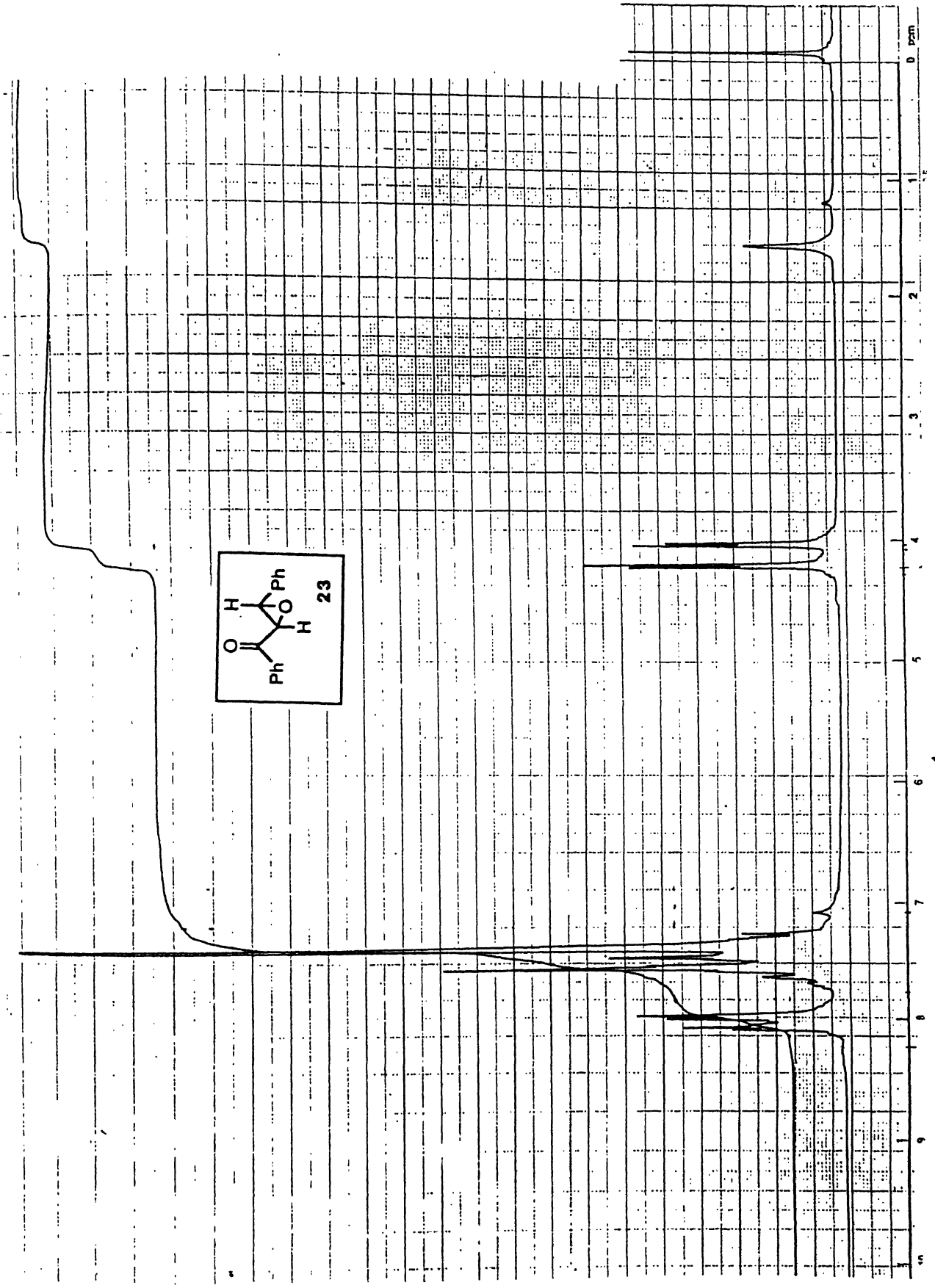


Fig. 4.1 ^{1}H NMR spectrum (80 MHz) of 23

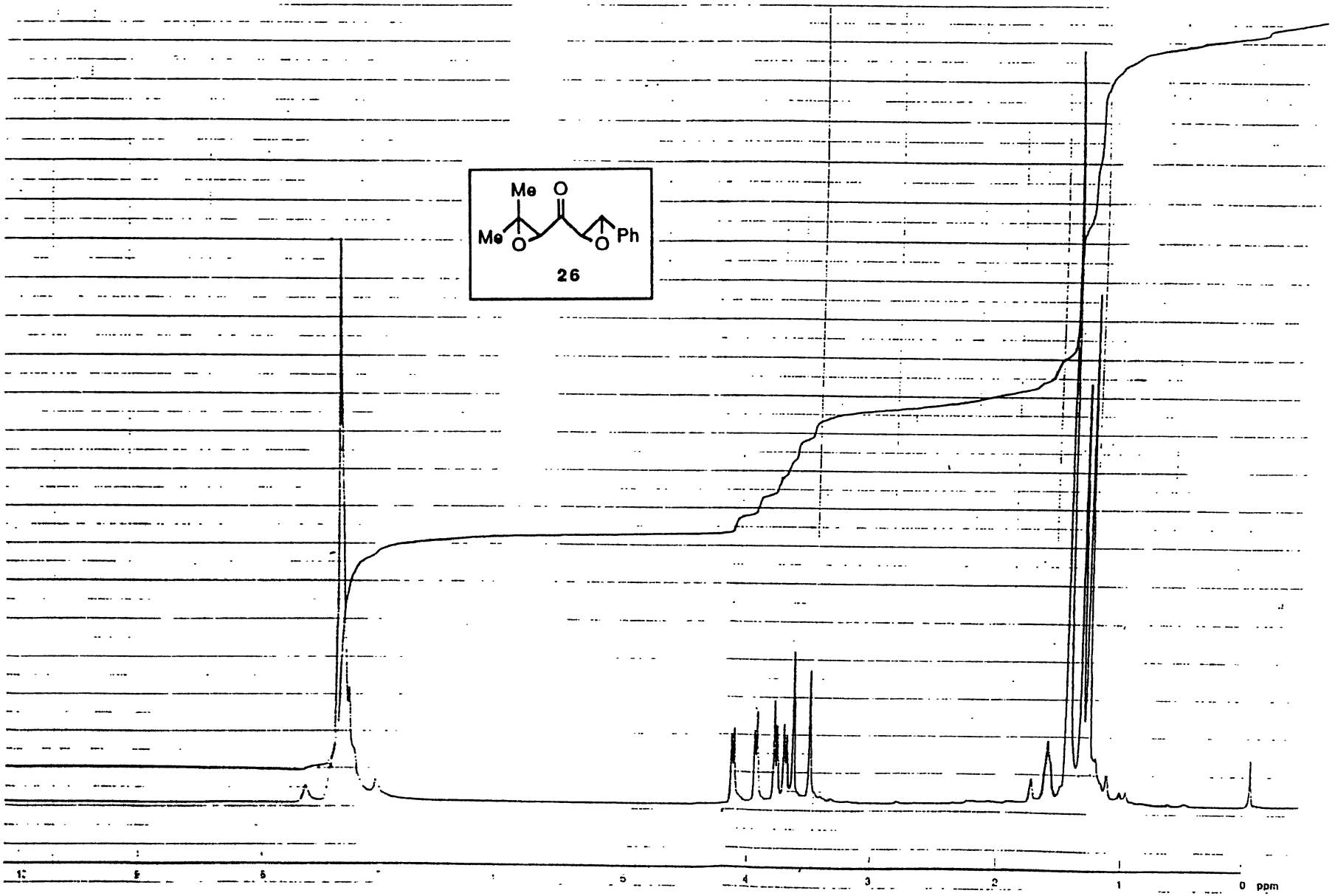


Fig. 4.2 ^{1}H NMR spectrum (80 MHz) of **26**

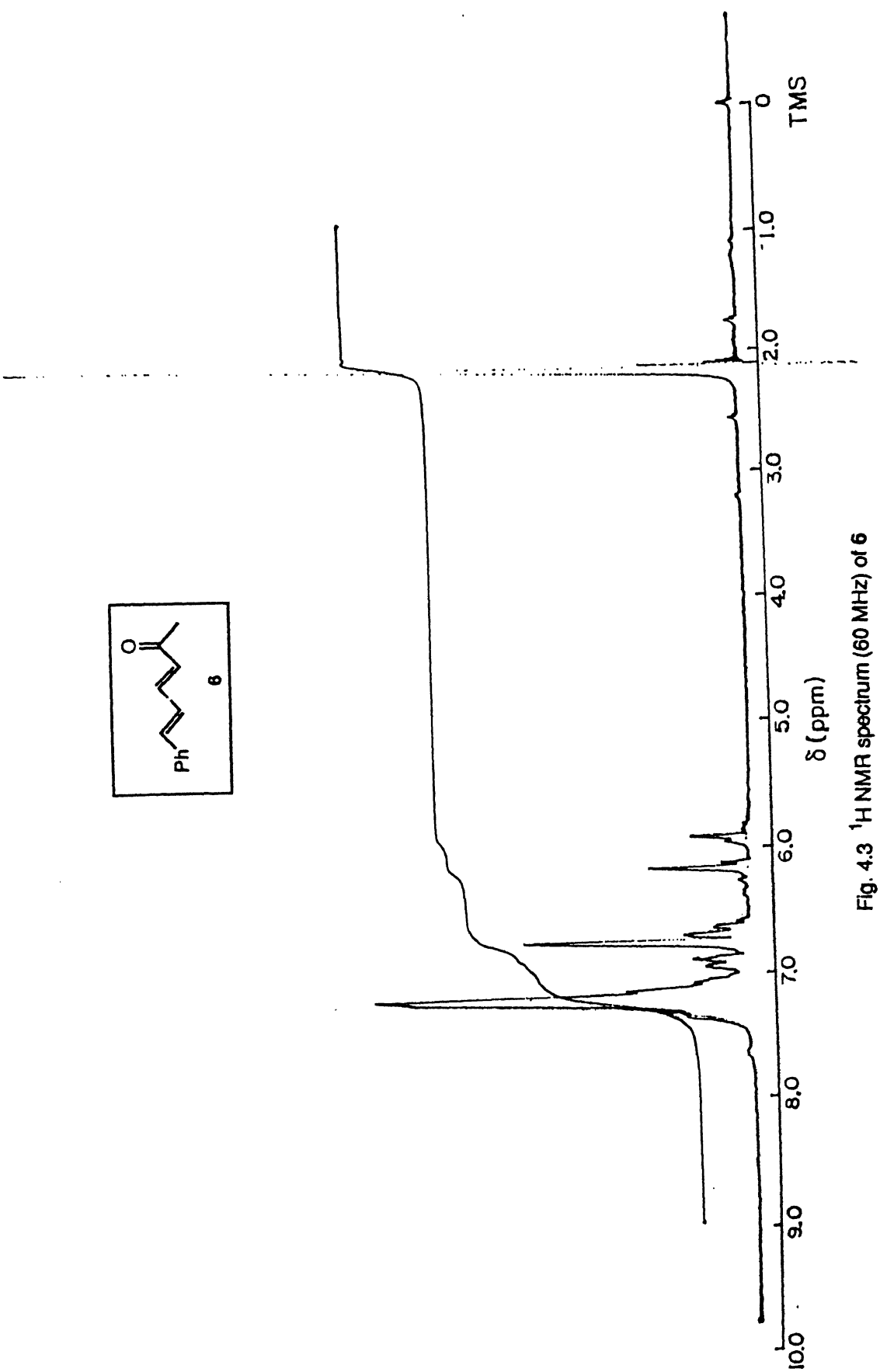


Fig. 4.3 ^{1}H NMR spectrum (60 MHz) of **6**

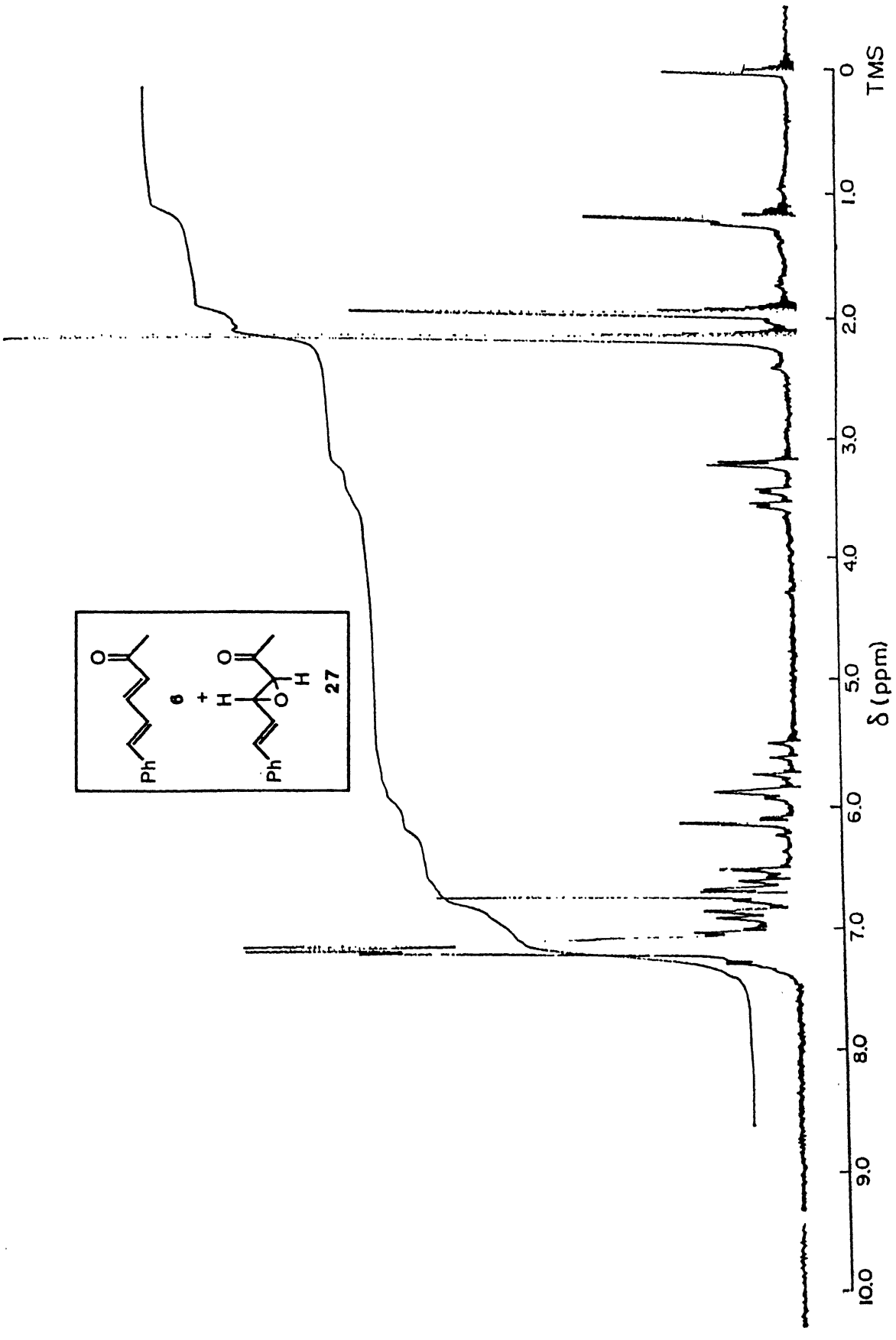


Fig. 4.4 ^{1}H NMR spectrum (60 MHz) of 6 & 27

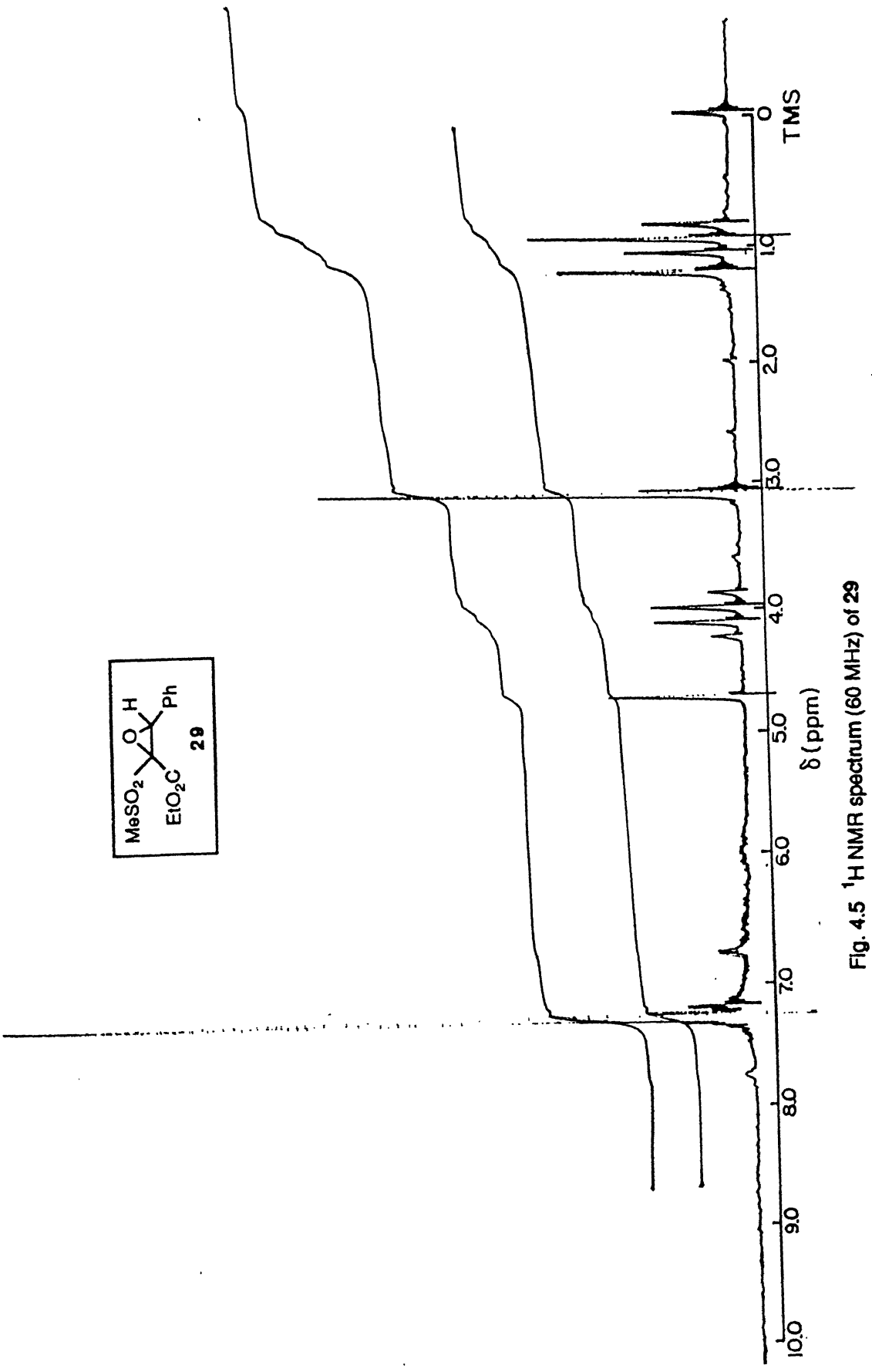


Fig. 4.5 ^{1}H NMR spectrum (60 MHz) of **29**

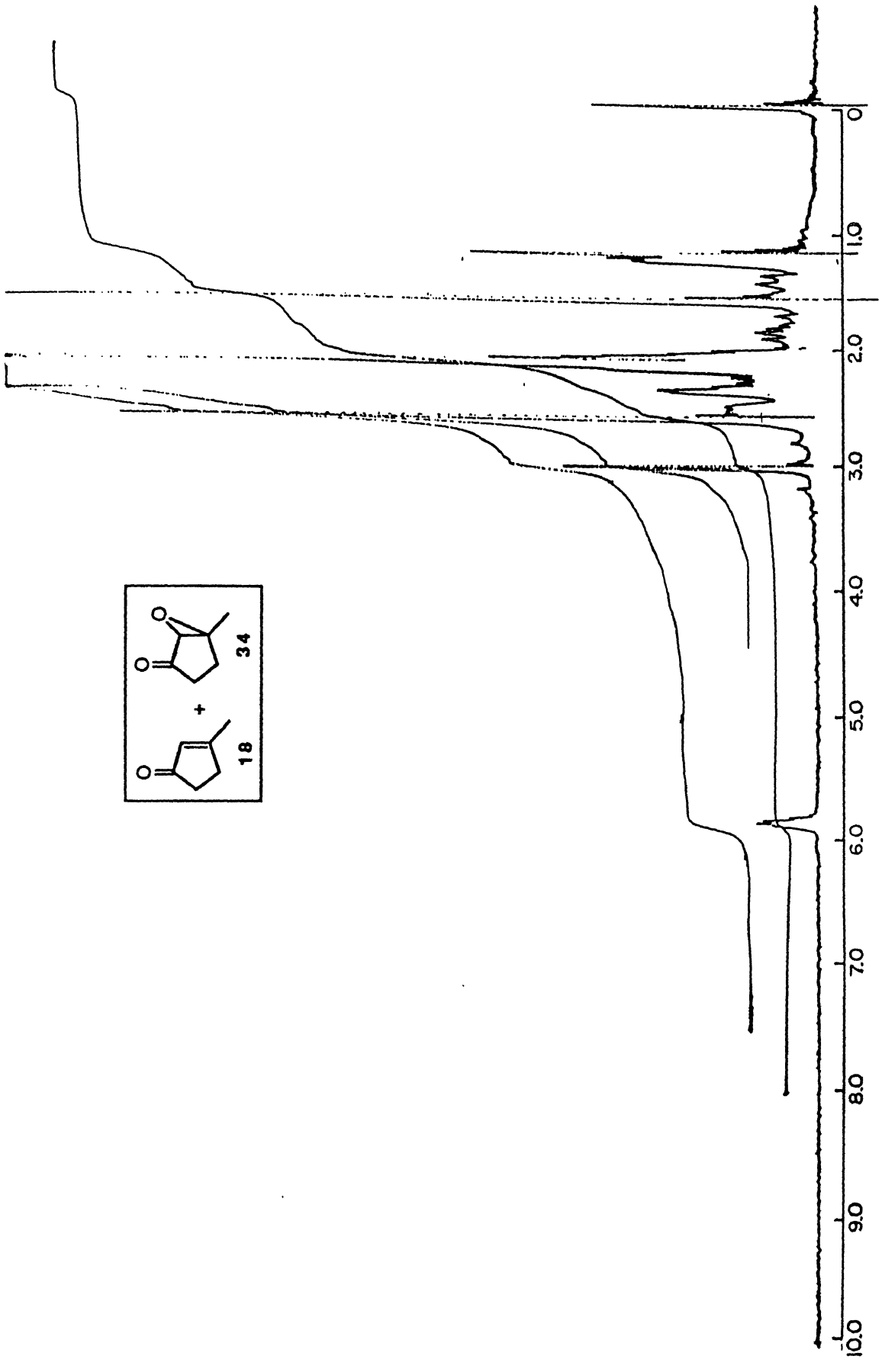


Fig. 4.6 ^{1}H NMR spectrum (60 MHz) of **18** & **34**

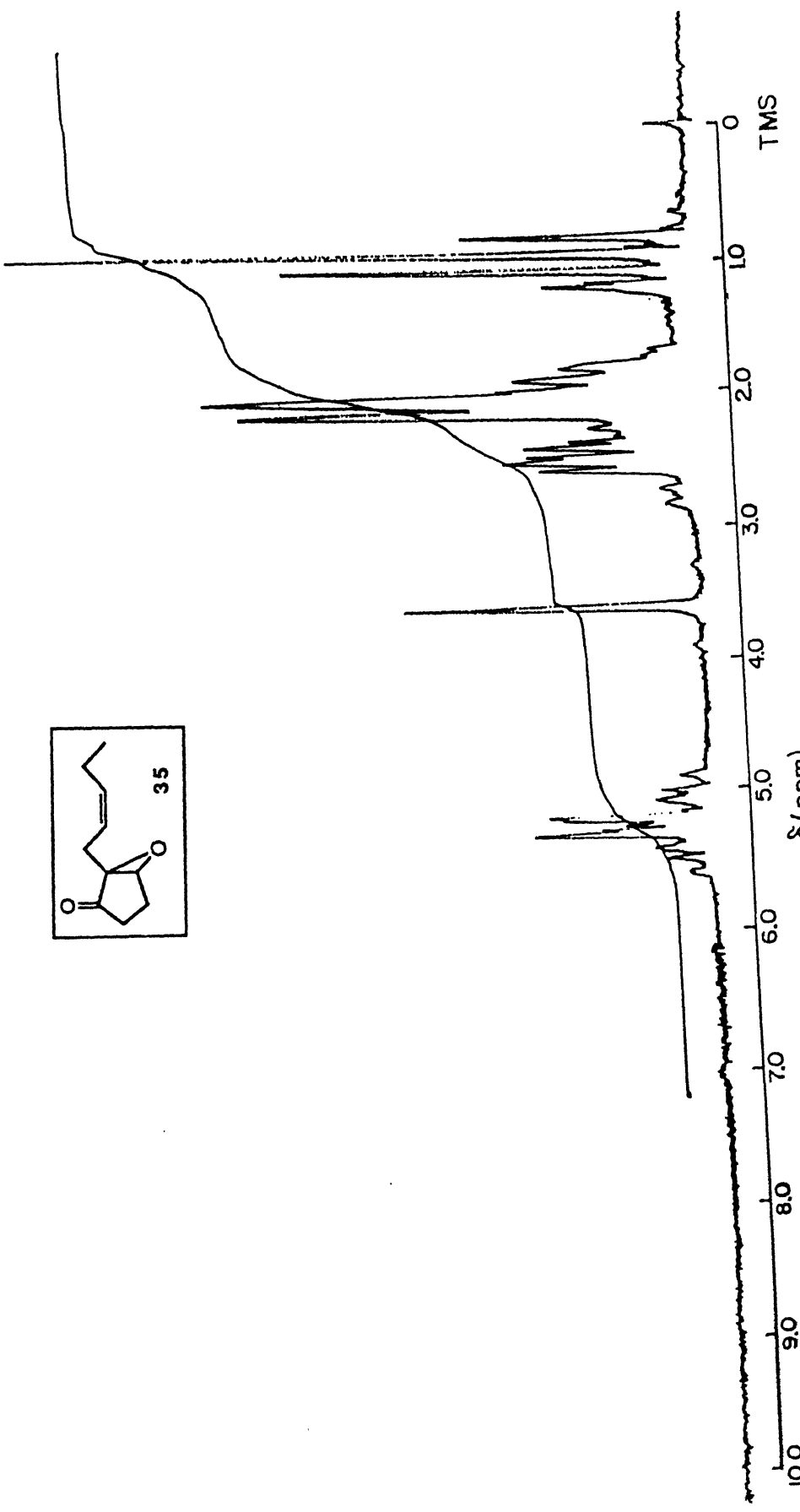


Fig. 4.7 ^{1}H NMR spectrum (60 MHz) of **35**

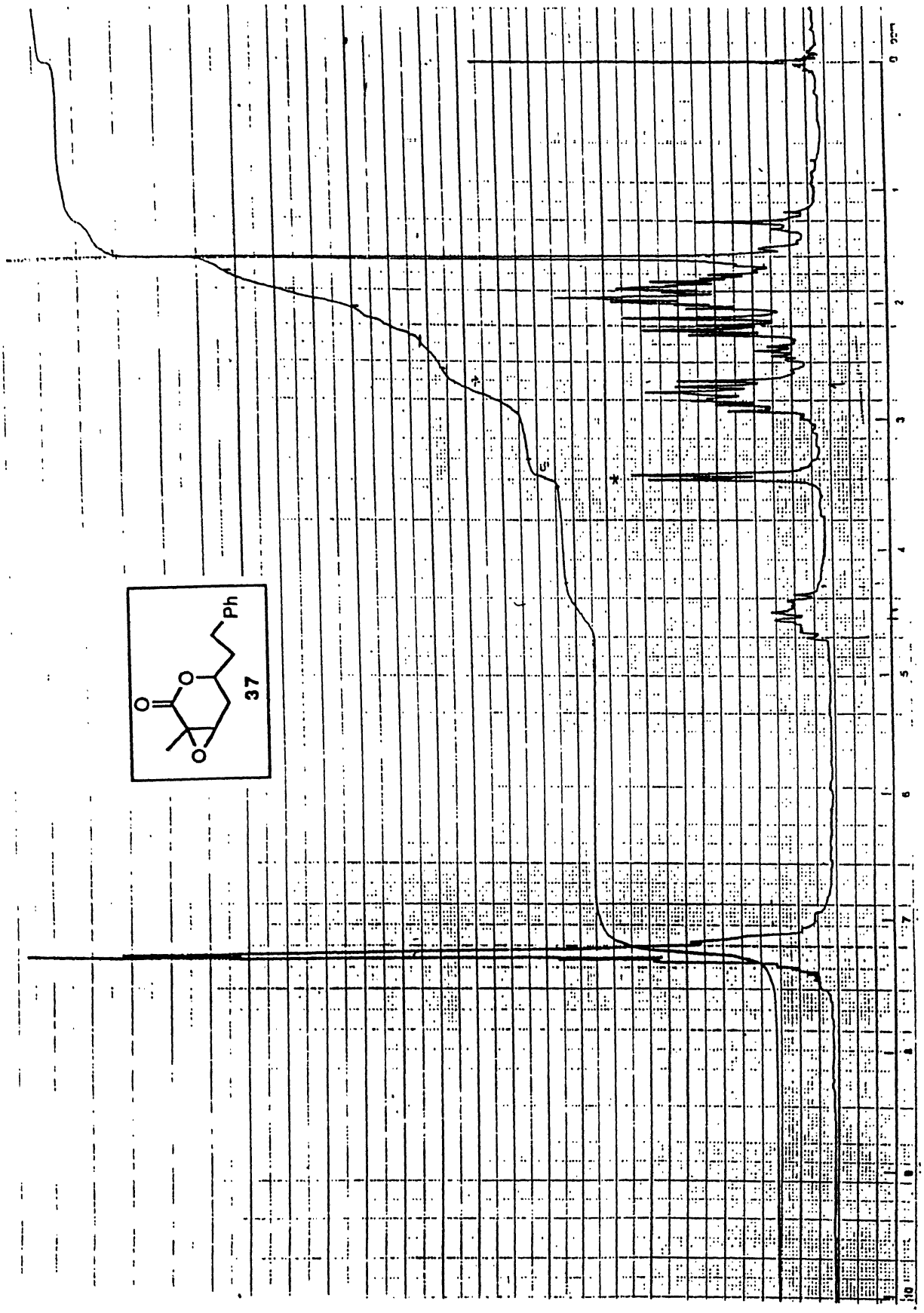


Fig. 4.8 ^{1}H NMR spectrum (80 MHz) of **37**

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CHANGING THE PHARMACOPHORE:

DBU Promoted Isomerisation of Unsaturated Lactones and its Application to the Construction of Structurally Interesting Species

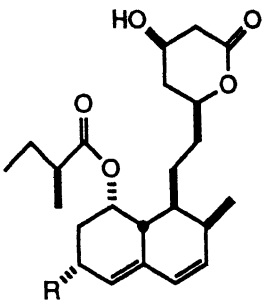
5.1 Introduction

Atherosclerosis is a complex and chronic disease involving gradual accumulation of lipids, collagen, elastic fibers, and proteoglycans in the arterial wall, resulting in intimal thickening. Since cholesterol esters and cholesterol are major components of atherosclerotic lesions, the interaction of the cholesterol-carrying lipoproteins in plasma with cells of arterial wall seem to be important. An increased level of total plasma cholesterol and an increase in major cholesterol carrying lipoprotein, low-density lipoprotein (LDL), are associated with an increased risk of developing atherosclerotic cardiovascular disease because the cholesterol of atherosclerotic plaques is derived from LDL[1]. Several hypocholesterolemic agents have been devised for use in lowering LDl levels[2].

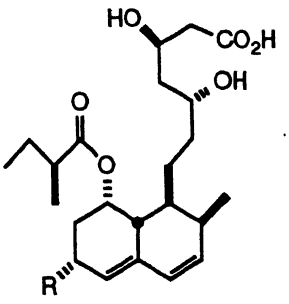
It has been clear for some time that a more attractive therapy might involve the regulation of *de novo* cholesterol biosynthesis. In humans, more than one-half of total body cholesterol is derived from this process[3]. An important step in the biosynthesis of cholesterol is the reduction of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) to mevalonic acid by the enzyme HMG CoA reductase (HMGR). This enzyme is the site of primary regulation for sterol biosynthesis. There has been intense interest in the possibility of controlling sterol biosynthesis pharmacologically as a way to cope with hypercholesterolemia and a few medicinal agents have been introduced that may have the effect of diminishing HMGR activity[4].

Compactin **1** and Mevonolin **2** have been shown to be effective in lowering plasma cholesterol levels in clinical trials[5-7] and it

is clear that these and related compounds have potential pharmacological use as hypocholesterolemic agents[8]. The active forms of compactin and mevinolin are the open chain dihydroxy acids **3** and **4**, respectively. The biological evaluation[10] of



1: R = H
2: R = Me



3: R = H
4: R = Me

various structural analogs of compactin and dihydromevinolin has established the fact that β-hydroxy-δ-lactone in its open β,δ-dihydroxy acid form is responsible for the bulk activity and the decalin moiety plays a purely hydrophobic role in binding the inhibitors to the enzyme.

5.2 Design Aspect

A drug designed with a view inhibiting a specific enzyme has three regions viz

(i) Pharmacophore: the key portion of the drug solely responsible for inhibition of enzyme action by interaction with the active site on enzyme e.g. β-hydroxy-δ-lactone segment in mevinic acids.

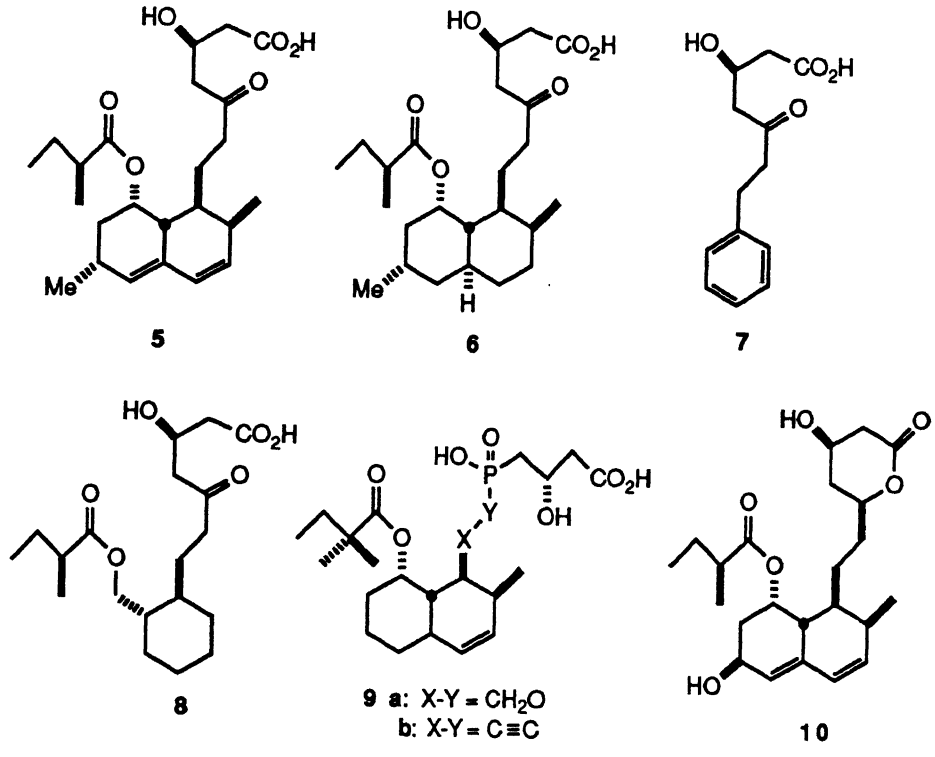
(ii) Template: responsible for binding or anchoring the drug to the enzyme surface or groove e.g. decalin portion in mevinic acids.

(iii) Linker or Spacer: the chain of atoms linking the pharmacophore and the template e.g. ethylene bridge in mevinic acids. This plays a significant role to carry the pharmacophore to the active site on the enzyme surface.

A drug binds to an enzyme principally by the Coulombic and H-bond attractive forces "in the binding region" and by the hydrophilic (or hydrophobic) attractive forces in the "hydrophilic (or hydrophobic) region".

Numerous approaches[10-16] reported in the literature for 'analog design' of mevinic acid are based on the concept of bringing changes in the (i) pharmacophore by replacing C-5 OH by carbonyl or hydroxyphosphinyl; (ii) linker i.e. ethylene bridge by replacing one of its CH_2's by oxygen atom or introducing unsaturation in it; (iii) decalin portion or replacing it with various anchoring hydrophobic aromatic and hydroaromatic surrogates and (iv) (S)-2-methylbutanoyl side chain. Some examples of structural analog of mevinic acid are collected below.

The 5-keto compounds **5** and **6**[10a] and **7**[10b] have IC_{50} values of 32 nM, 1 nM and 1.3 mM, respectively, compared with IC_{50} values of 13 nM, 1.6 nM and 0.6 mM for the corresponding 3(R),5(R)-dihydroxy acids. Compound **8**[10b] inhibits HMGR with IC_{50} = 320 μM, compared to the corresponding value of 32 nM for compactin ketone, **5**. The difference by a factor of 10^4 in these two inhibitors corresponds to the difference in binding energy of 5.5 kcal mol^{-1}, for each of the four carbons of **5** that are missing in the analog **8**. This quantitative difference is consistent with the idea that decalin moiety in mevinic acids plays a purely hydrophobic role in binding the inhibitors to the enzyme.

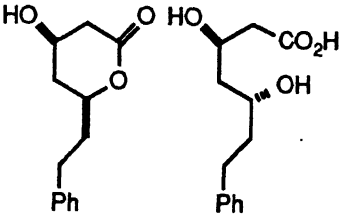


Karanewsky and Badia[11a] have recently demonstrated that the hydroxyphosphinyl analog **9** lead to enhanced binding to the active site of HMGR.

The structure-activity relationship (SAR)[12] of dozens of analogs, prepared by replacing the decalinic moiety by various aromatic and hydroaromatic segments, led to the development of a series of potent HMGR inhibitors in which the decalinic moiey is replaced by substituted biphenyls. Serizawa et al[13] have reported that compound **10**, which has an equatorial hydroxy group at C-3, has about the same inhibitor activity as mevinolin.

We contemplated to prepare an analog of mevinic acid for its biological evaluation and focussed our attention to modify the key pharmacophore i.e. β-hydroxy-δ-lactone in **11**. Our concept is

based on the philosophy of bringing alteration in the interatomic distances in the pharmacophore. Since the active form for



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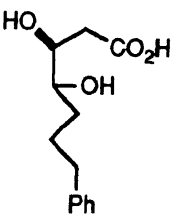

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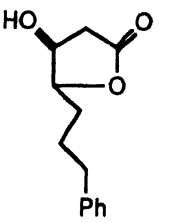


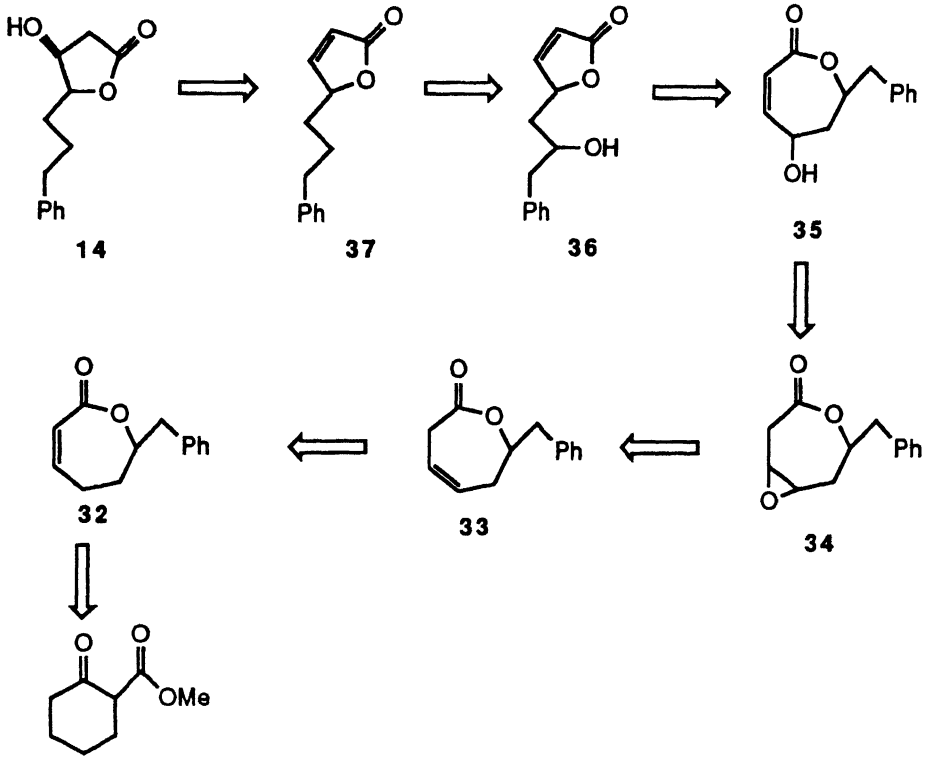
14

inhibition of HMGR is the open chain dihydroxy acid **12**, it is worth studying the biological activity of **13** in which 5-hydroxy group has been shifted to position-4. The cyclic form of **13** is the β-hydroxy-γ-lactone **14**. We wished to synthesise **14** employing our methodologies for epoxidation of α,β-unsaturated lactones (see the preceding chapter) and deconjugative isomerization.

5.3 Retrosynthesis

The retrosynthetic strategy (Scheme 5.3.1) devised for 4-hydroxy-5-(3-phenylpropyl)tetrahydrofuran-2-one **14** envisages it to derive from the enelactone **37** following a two step sequence, namely (a) epoxidation and (b) regioselective α-cleavage of the oxirane. The compound **37** may be conceived to obain from the hydroxy enelactone **36** by the application of Robin's radicalar deoxygenation protocol[17]. Construction of **36** requires opening of the 7-membered lactone ring in **35** following its recyclization to a γ-lactone. The preferential formation of γ-lactone over a

Scheme 5.3.1



seven-membered ring analog is well established in literature. The material **35** is envisioned to derive from **34** after the latter has been subjected to deprotonation by a non-nucleophilic base. The enelactone **32**, itself drivable from 2-carbomethoxy cyclohexanone (see Scheme 5.4.6) or cyclohexanone, could be transformed into **34** by the employment of a two step protocol involving (a) deconjugative isomerization to **33**, and (b) its oxidation by per-acids.

Shorter routes to prepare the mevinic acid analog **14** can also be envisioned. Our interest to pursue the above warrants comments:

(a) while studying the epoxidation of enelactones by t-BuOOH and DBU, we obsessed decongative isomerization of **32** into **33**,

(b) we felt observed to use our own methodology on the epoxidation of enlactones.

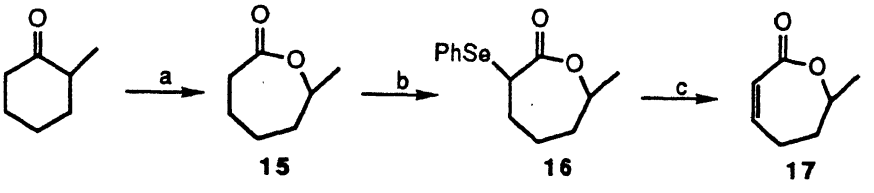
5.4 Results and Discussion

5.4a Deconjugative isomerization of enelactones with DBU

During the course of study on the exploration of epoxidation of α,β-unsaturated lactones using t-BuOOH and DBU in dichloroethane[18e], we discovered 3,4-dehydro-7-methyl-2-oxepanone **17** undergoing deconjugation to give, other than the α,β-epoxy lactone, the 4,5-dehydro isomer **18** in about 50% yield (expt. 4.3.31 of Chapter 4). In a subsequent experiment in which the enelactone **17** was treated with 1 equivalent of DBU in $CHCl_3$, a clean transformation to **18** was noticed in less than 5 hours. Extended reaction did not lead to any equilibrium mixture.

The conjugated enelactone **17** was prepared from 2-methyl cyclohexanone (Scheme 5.4.1) by Baeyer-Villiger oxidation

Scheme 5.4.1



(a) Baeyer-Villiger oxidn.; 80% (b) LDA, THF, - 80 °C, PhSeBr; 70%
(c) H_2O_2, pyridine; 76%.

followed by the introduction of α,β-unsaturation using selenium chemistry as described earlier in Chapter 3. The structures of

the intermediates (**15** and **16**) have been secured from spectral means and elemental analyses. ^{1}H NMR spectra of **15** and **16** are given in Figs. 5.1 and 5.2, respectively. ^{1}H NMR spectrum of **17** (Fig. 5.3) displays characteristic signals at ppm 6.6-6.1 (td, 1H, J = 12 and 4 Hz), 6.0 - 5.6 (td, 1H, J = 12 and 1 Hz), 4.7- 4.1 (m, 1H) and 1.35 (d, 3H, J = 6 Hz). IR (1700 cm^{-1}) and mass spectrum (m/z = 126, M^+ and elemental analysis are in accord to the formulation of **17**.

The characteristic signals of **18** in its ^{1}H NMR spectrum (Fig. 5.4) appear at ppm 6.0-5.3 (m, 2H, olefinic protons), ppm 4.0-3.5 (dd, 1H, J = 16 and 3 Hz, C-3 $\underline{H}$), ppm 3.6-2.8 (dd, 1H, J = 16 and 6 Hz, C-3 $\underline{H}$), 5.2-4.7 (m, 1H, -OC$\underline{H}$$CH_3$), and 1.4 (d, 3H, J = 6.0 Hz, -OCHC$\underline{H}_3$). IR (1725 cm^{-1}), and mass spectrum (m/z = 126, M^+) and elemental analysis are also supportive.

Encouraged from the above findings we became interested to investigate the scope of DBU promoted deconjugation of enelactones. Inspite of many uses of this hindered base in synthesis[18], this application has not been reported before. The deconjugation of α,β-unsaturated carbonyls has traditionally been accomplished by the use of bases such as

(i) potassium hexamethyldisilazide $KN(SiMe_3)_2$[19] in THF at -78 ^oC

(ii) LDA[20] in THF/HMPT at -70 ^oC

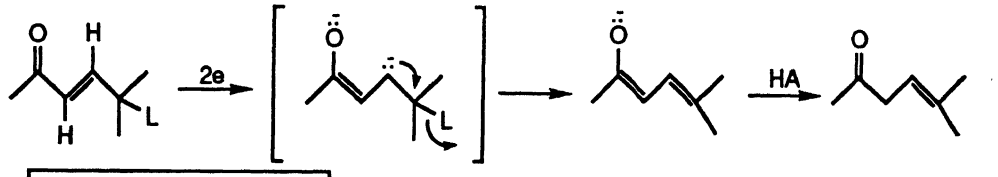
(iii) $KOBu^t$ in Bu^tOH[22] at rt, and

(v) KNH_2 in liquid NH_3[23].

The enolate, so generated, is kinetically quenched (aq NH_4Cl or aq HCl) to receive the products. Lansbury et al[24] have reported that α,β-unsaturated carbonyl compounds containing good leaving

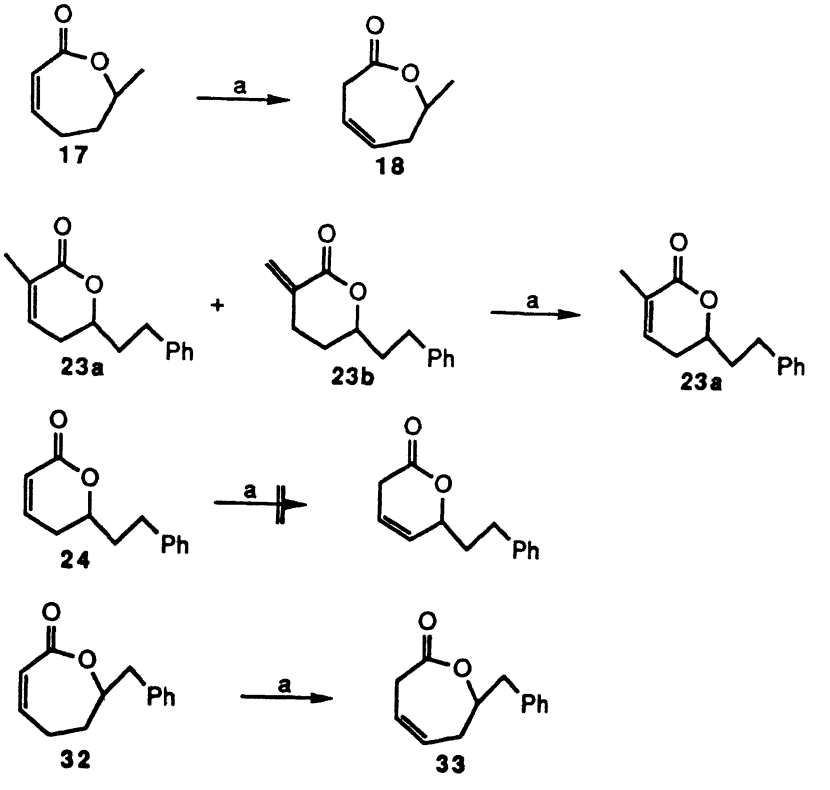
group are susceptible to dissolving metal reductive elimiantion[25], with the resultant dienolate able to survive further reduction by means of appropriate quenching techniques (Scheme 5.4.2).

Scheme 5.4.2



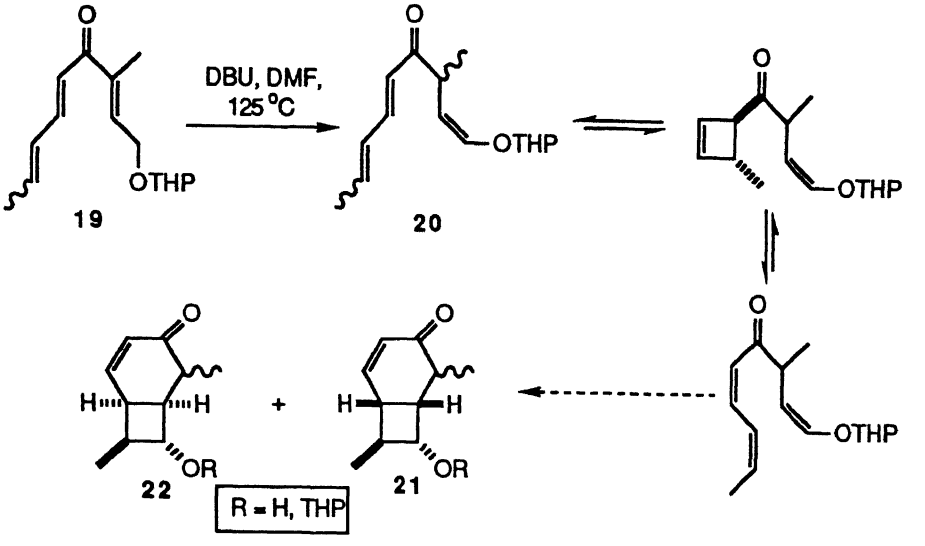
To test the generality of DBU-promoted deconjugation of enelactones, few enelactones (Scheme 5.4.3) were submitted to

Scheme 5.4.3



similar reaction conditions. The α,β-unsaturated esters were not chosen because Marsaioli et al[26] did not notice, while investigating the acetyl cleavage by DBU, any deconjugation of α,β-unsaturated moiety which was present in one of the substrates studied. Recently, Snider and Harvey[27] have speculated a DBU-promoted deconjugation of an acyclic enone **19** into the corresponding deconjugated species **20** to account for the former's isomerization to bicyclo[4.2.0]octenones **21** and **22** (Scheme 5.4.4).

Scheme 5.4.4

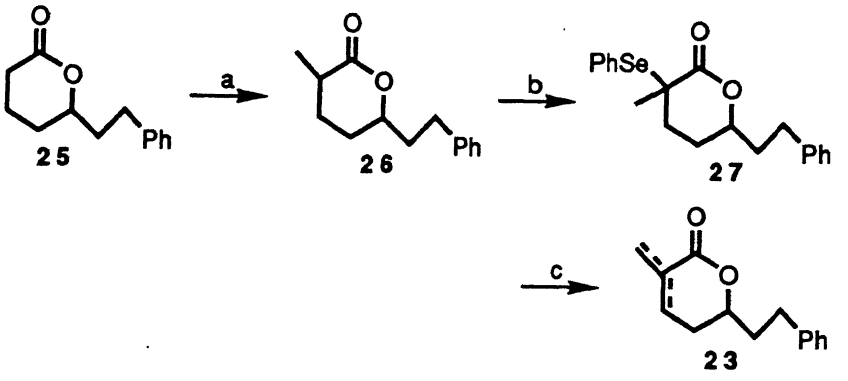


In a mixture of 3-methyl-3,4-dehydro-6-(2-phenylethyl)tetrahydropyran-2-one **23a** and 3-methylidene-6-(2-phenylethyl)tetrahydropyran-2-one **23b**, presence of only *endo* enlactone **23a** in the reaction mixture after 10h revealed that *exo* enelactone **23b** had undergone smooth isomerization into its *endo* counterpart **23a**. Further deconjugation in **23a** did not occur. Also, the enelactone **24** behaved neutral, indicating that the deconjugation of

α,β-unsaturated valerolactones is an energetically uphill process under the DBU conditions.

The preparation of enelactone **24** has been described earlier in Chapter 3 (expt. 3.3.5). For the preparation of a mixture of

Scheme 5.4.5



(a) LDA, THF, - 80 °C, MeI, HMPT; 67% (b) LDA, THF, - 80 °C; 78%
(c) H_2O_2 , pyridine, CH_2Cl_2 ; quantitative.

the *endo* and the *exo* enelactones **23(a,b)**, lithium enolate of lactone **25** (from expt. 3.3.3) generated at -80 °C was quenched with methyl iodide to furnish α-methyl lactone **26**. The formulation of **26** had been arrived at by means of spectral data and elemental analysis (cf expt. 5.5.6). The compound **26**, on selenenation followed by selenoxide elimination as described earlier in Chapter 3, give a mixture of the *endo* and *exo* lactenones **23(a,b)**. The intermediate selenolactone **27** was ascribed the structure based on spectral data (cf expt. 5.5.7). ^{1}H NMR spectrum (Fig. 5.5) displayed a multiplet at ppm 6.6 (1H) due to olefinic proton of *endo* enelactone **23a** and two quartets at ppm 6.5 (1H, J = 2 Hz) and 5.6 (1H, J = 2 Hz) due to the olefinic

2-carbomethoxy cyclohexanone was alkylated with benzylbromide in presence of DBU[28] to give **28**. This was dealkyldecarboxylated (LiCl/DMF) to give **29**. The material **29** could also be prepared from direct benzylation of cyclohexanone in presence of LDA. The spectral data (^{1}H NMR and IR) and elemental analyses are in agreement with the formulations of **28** and **29** (cf expt. 5.5.10 and 5.5.11). Baeyer-Villiger oxidation of **29** afforded the lactone **30** which showed in its ^{1}H NMR spectrum (Fig. 5.7) a multiplet at ppm 4.3 (1H) due to >C<u>H</u>O. IR (1720 cm^{-1}), mass spectrum, and elemental analysis support the structure **30** further. The lactone **30** gave, on selenenation, a 1:1 mixture of *cis* and *trans* selenolactones **31a** and **31b** in a combined yield of 72%. The low yield of selenenation of 7-membered lactones as compared against >90% for that of 6-membered lactones may be attributed to the decreased activity of ring carbonyl group caused by a shielding effect due to the ring puckering. The structural identity of **31a** as the *cis* and **31b** as the *trans* isomer followed from the difference in chemical shifts of protons of ring position 7. The ^{1}H NMR spectrum (Fig. 5.8) of **31a** showed diagnostic resonances at ppm 4.50 (m, 1H) and 4.20 (dd, 1H, J = 12 and 2 Hz) corresponding to hydrogens on positions C-7 and C-3, respectively. The respective shifts for these protons in **31b** (Fig. 5.9) are at ppm 5.25 (1H, m) and 4.25 (t, 1H, J = 4 Hz). Unlike **31a**, the benzeneselenenyl group, being *cis* to the hydrogen on C-7, pushes the latter appear downfield on NMR scale presumably due to anisotropy effects. Further confirmation to structural identities of **31a** and **31b** come from the IR (1710 cm^{-1}) and mass spectral data. Dehydroselenenation of **31a** and **31b** produced the requisite conjugated enelactone **32**. Characteristic ^{1}H NMR

resonances (Fig. 5.10) at ppm 6.6-6.3 (d, 1H, J = 12 and 4 Hz), 6.1-5.9 (td, 1H, J = 12 and 1.2 Hz), and 4.4-3.6 (m, 1H), IR absorption at 1700 cm^{-1}, mass spectrum, and elemental analysis are indicative.

The ^1H NMR spectrum of **33** (Fig. 3.11) showed multiplets between ppm 5.9 and 5.3 (2H) due to the olefinic protons and between 5.10 and 4.70 (1H) due >C<u>H</u>O along with other characteristic signals. In further agreement to this formulation are the IR (1720 cm^{-1}) and mass spectral (cf expt. 5.5.15).

Interestingly, in an equilibrium study that we carried out with the conjugated material **32** and monitored by ^1H NMR at various intervals, we noticed that after the initial 6h, there is a continuous fall in the concentration of the deconjugated species **33** with a corresponding rise in the concentration of the conjugated material **32**, setting an equilibrium (60:40, in favor of the unconjugated isomer) after about 25h. When a similar equilibrium study was carried out starting with the unconjugated material **33**, the attainment of the above equilibrium took longer time (~ 50h). These equilibrium studies are clearly indicative of small energy difference in the two isomers **32** and **33**; the latter being more stable. This is in contrast to the general belief that the α,β-unsaturated esters and lactones are more stable than their deconjugated isomers.

5.4b Attempts at the synthesis of pharmacophore 14 and application of deconjugative isomerization to the construction of synthons of natural products

As has already been mentioned in the retrosynthesis

(Scheme 5.3.1), the oxirane **34** was to be employed as an important substrate in the architecture of pharmacophore **14**.

Having the requisite olefin **33** in hand, the task of formation of its oxirane **34** was taken up. Oxidation of **33** with perbenzoic acid gave a mixture of two species having R_f values 0.5 and 0.1, (30% EtOAc in Pet. ether as eluant) in respectively, 2:1 proportion (based on actual isolation by chromatography). The less polar material was assigned the structure **34** on the grounds of disappearance of olefinic resonances (ppm 5.9-5.3 (m, 2H) in its ^{1}H NMR spectrum (Fig. 5.12) and appearance of resonances at ppm 3.29 (m, 1H) and 2.96 (dd, 1H, J = 13 and 4 Hz) arising due to the oxirane ring protons. IR (1720 cm^{-1}), mass spectrum, and the elemental analysis are in tune with the formulation **34**.

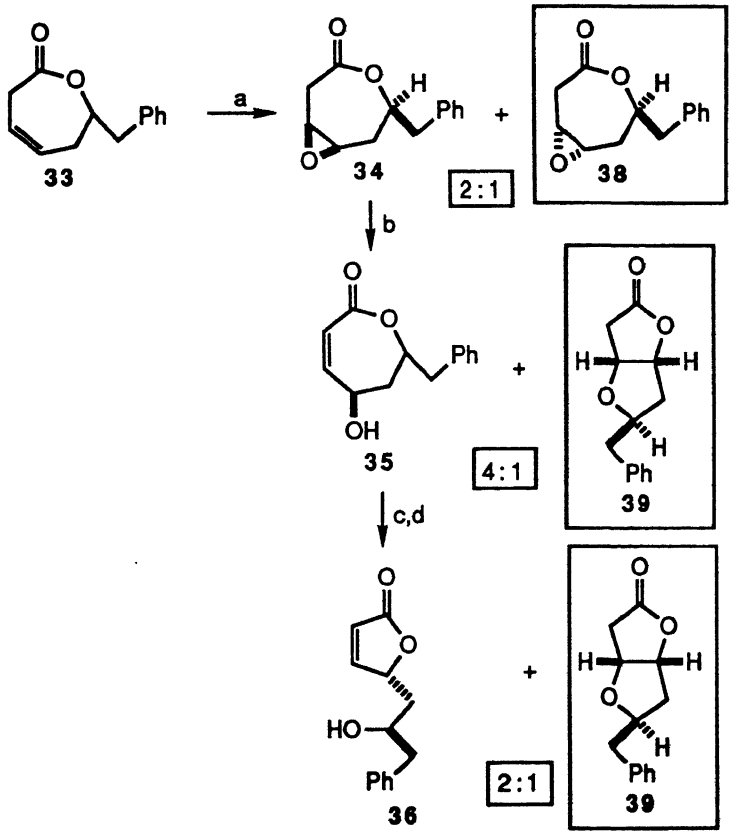
^{1}H NMR spectrum (Fig. 5.13) of the more polar material displayed characteristic resonances at ppm 4.66 (m). 3.41 (usymm. d, J = 15 Hz), 3.3 (dd, J = 15 and 6 Hz), 3.2 (m), 3.05 (dd, J = 13 and 6 Hz), 2.78 (dd, J = 13 and 6 Hz), 2.37 (d, J = 17 and 12 Hz) and 2.18 (m) with approximate relative integral ratio as 5:1:1:1:2:1:1:1:1. These fit well in the oxirane structure **38**, an isomer of **34**. The ^{13}C NMR spectrum (Fig. 5.14) exhibited, apart from aromatic carbons, three methylene carbons (ppm 31.4, 35.4 and 41.8), three methine carbons (ppm 50.5, 52.5 and 71.0), and one carbonyl carbon (ppm 168.2) (as revealed by DEPT), which supports the oxirane structure **38**.

The resonances, in the ^{1}H NMR spectrum at ppm 4.66, 3.41, 3.3, and 3.2 are assigned, respectively, to >C<u>H</u>O, pseudoequatorial-<u>H</u> at C-3, pseudoaxial-<u>H</u> at C-3, anf 2 protons of oxirane ring. The resonances at ppm 3.05 and 2.78 are due to the

benzylic hydrogens. IR (1730 cm^{-1}), mass spectrum, and the elemental analysis are consistent with the above formulation. Since, in the ^1H NMR spectrum, >C<u>H</u>O resonates downfield (ppm 4.66) in compound **38** as compared to that in **34** (ppm 4.31), **38** appears to the *trans* isomer in which the said proton experiences anisotropic effect of the oxirane ring oxygen.

To accomplish the deprotonation of oxirane **34**, K_2CO_3 in DMF[29] was employed (Scheme 5.4.7) of the two products, the more polar

Scheme 5.4.7



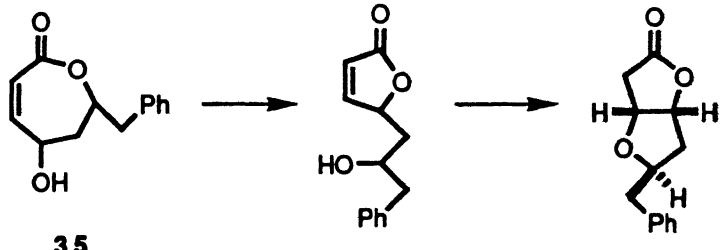
(a) $PhCO_3H$, $CHCl_3$; 90% (b) K_2CO_3, DMF, rt; 95% (c) 2% aq NaOH, THF, 1h (d) acidification, 30 min; 84% for steps c&d.

was uv active and hence indicative of the presence of α,β-unsaturated carbonyl chromophare and hence **35**. ^1H NMR

spectrum (Fig. 5.15) of **35** displays resonances at ppm 6.2 (dd, 1H, J = 12 and 3 Hz) and 5.7 (dd, 1H, J = 12 and 1 Hz), and 4.9 - 4.2 (m, 2H) arising from the β- and α-olefinic hydrogens of the unsaturated system, and the hydrogens on the carbons attached to the oxygen atoms. Consistent with the formulation **35** are the IR (3420 cm^{-1}, OH, 1695 cm^{-1}, conjugated carbonyl) and mass spectra, and the elemental analysis.

For the structural identification of the less polar material, IR and mass spectra proved very helpful. IR spectrum showed a strong band at 1770 cm^{-1} which is diagnostic of saturated 5-membered lactone. In the ^1H NMR spectrum (Fig. 5.16), resonances at ppm 5.10 (t, J = 4 Hz), 4.81 (t, J = 4 Hz) and 4.37 (m) are indicative of the presence of three types of >CHO. These resonances taken together with the absence of OH absorption in the IR spectrum and olefinic hydrogens in the ^1H spectrum conform to the structure **39**. The above ^1H resonances arise due hydrogen marked Ha, Hb, and Hc, respectively. Mass spectrum and elemental analysis are in full accord to the above formulation **39**. This type of transformation (**34** to **39**) has earlier been observed under Baeyer-Villiger conditions[30].

Scheme 5.4.8



The formation of **39** may be conceived via the hydroxy

enelactone **36** which undergoes intramolecular Michael addition (Scheme 5.4.8).

Alkaline hydrolysis of **35** followed by acidification furnished a 2:1 mixture of the desired hydroxy enelactone **36** and the above bicyclic material **39** (TLC).

The structural identity of uv active material **36** rests upon ^{1}H NMR [Fig. 5.17; ppm 7.6 (dd, 1H, J = 5 and 1.5 Hz), 6.1 (dd, 1H, J = 5 and 2.0 Hz), 5.3 (tt, 1H, J = 6.5 and 1.5 Hz), and 4.0 (m) due to the hydrogens designated Ha, Hb, Hc and Hd, respectively], IR [3440 (OH), 1740 cm^{-1} (unsaturated carbonyl in γ-lactone)] and mass spectra, and elemental analysis.

To reach the target, material **36** may be conceived to put to use in two ways, viz

(i) epoxidation of enelactone, deoxygenation, and regioselective α-cleavage of the oxirane; in that order and

(ii) deoxygenation, epoxidation, and regioselective α-cleavage of the oxirane; again in that order.

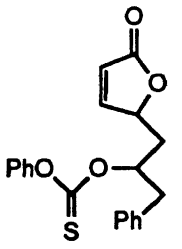
Route (i) could not be feasible because cyclization to the bicyclic material **39** was found much faster than the anticipated oxidation in an experiment in which **36** was allowed to react with t-BuOOH and DBU in dichloroethane[18e].

We next contemplated route (ii) and Robin's deoxygenation protocol[17] was called in. To prepare the phenylthionocarbonate ester **41**, alcohol **36** was reacted with phenoxythiocarbonyl chloride (PTC-Cl) and pyridine in dichloromethane in presence of catalytic amounts of DMAP. This furnished the bicyclic material **39** (46%) and the unreacted starting alcohol. In another bid, PTC-Cl,

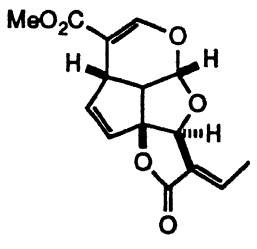
pyridine and DMAP (catalytic amount) were taken in dichloromethane and a solution of alcohol was added slowly over a period of 2h (syringe pump), no improvement in the reaction was observed. Change of solvent from CH_2Cl_2 to CH_3CN was also not fruitful.

In another experiment, introduction of oxirane ring at an earlier stage was envisioned and the hydroxy enelactone **35** reacted with t-BuOOH and DBU in dichloroethane. Only, the bicyclic material **39** was received.

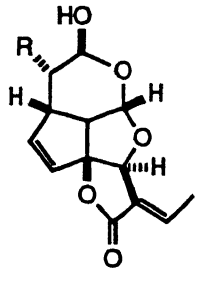
Literature survey revealed that the bicyclic ring **39** is present in plumeria and allamanda iridoids such as plumericin **42**, allamcin **43**, and allamandin **44** which exhibit cytotoxic, antileukemic, antimicrobial, and antifungal properties[31,32]. Other natural products which possess this skelton are delesserine **45** and dilaspirolactone **46** which exhibit anticoagulant properties[32], and piptosidin **47**[34]. Functionalised γ-lactones are important building blocks[35] in natural products synthesis.



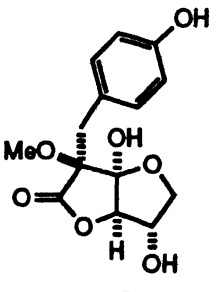
41



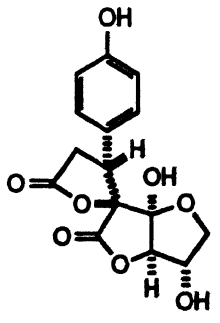
42



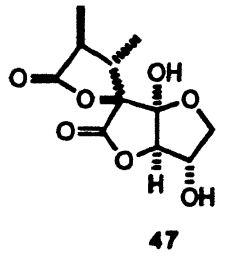
43: R = H
44: R = CO_2Me



45



46



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General Considerations: All chromatogrhic separations were performed over silica gel (100 - 200 mesh) using petroleum ether (60 - 80) and ethyl acetate mixtures as eluant. Ether, wherever used, stands for diethyl ether. The organic extracts were dried over anhydrous Na_2SO_4. Commonly used abbreviations are used throughout. Solvents used in this study were dried as per established procedures. Product(s) solutions were freed of solvents under reduced pressure on rotovap.

Radial chromatography was performed over silica gel GF_{254} coated on circular plates and using model 7924T CHROMATOTRON, Harrison Research (USA).

For slow additions, syring pump model 341B, Sage Instruments, Division of Orion Research Incorporated, 529 Main Street, Boston, MA 02129 USA was employed.

Details of other instruments used are the same as described in Section 3.3 of Chapter 3.

Baeyer-Villiger oxidation, selenenation and dehydroselenation were performed following the procedures as described in Section 3.3 of Chapter 3.

5.5.1 7-Methyl-2-Oxepanone 15

Baeyer-Villiger oxidation of 2-methylcyclohexanone (0.672 g, 6.0 mmol) furnished **15** (0.615 g, 80%).

^{1}H NMR (60 MHz) : ppm 4.8-4.1 (m, 1H, -OC$\underline{H}$CH$_3$), 2.9-2.3 (m, 2H, -C$\underline{H}_2$C(O)-), 2.2-1.9 (m, 6H, 3xC$\underline{H}_2$), 1.3 (d, 3H, J = 6 Hz, -C$\underline{H}_3$).

IR (neat), ν_{max} : 1720 (C = O), 1450, 1170, 1020, 850 cm^{-1}.

Analysis calcd.for $C_7H_{12}O_2$: C, 65.62, H, 9.37;

Found : C, 65.51, H, 9.42%.

5.5.2 3-Benzeneselenenyl-7-methyl-2-oxepanone 16

Selenenation of **15** (0.128 g, 1.0 mmol) gave **16** (0.20 g, 70%).

^{1}H NMR (60 MHz) : ppm 7.6-6.9 (m, 5H, Ar$\underline{H}$), 5.1-4.5 (m, 1H, -OC$\underline{H}$CH_3), 4.15-3.9 (unsymm.t, 1H, -C$\underline{H}$SePh), 2.3-1.5 (m, 6H, 3xC$\underline{H}_2$), 1.3 (d, 3H, J = 6 Hz, -C$\underline{H}_3$).

IR (neat), ν_{max} : 1705 (C = 0), 1250, 1030 and 735 cm^{-1}.

Mass (m/z) : 283 (M^+).

Analysis calcd.for $C_{13}H_{16}O_2Se$: C, 55.12, H, 5.65;

Found : C, 55.00, H, 5.72%.

5.5.3 3,4-Dehydro-7-methyl-2-oxepanone 17

Dehydroselenation of **16** (0.16 g, 0.56 mmol) furnished **17** (0.054 g, 76%).

^{1}H NMR (60 MHz) : ppm 6.6-6.1 (td, 1H, J = 12 and 4 Hz, -$\underline{H}$C = CHC(O)-), 6.0-5.6 (td, 1H, J = 12 and 1 Hz, -CH=C$\underline{H}$C(O)-), 4.7-4.1 (m, 1H, -OC$\underline{H}$CH), 2.7-2.2 (m, 2H, -C$\underline{H}_2$CH=CH-), 2.2-1.7 (m, 2H, >C$\underline{H}_2$), 1.35 (d, 3H, J = 6 Hz, -C$\underline{H}_3$).

IR (neat): ν_{max} : 1700 (C = 0), 1400, 1290, 1200, 1060 and 1000 cm^{-1}.

Mass (m/z) : 126 (M^+).

Analysis calcd.for $C_7H_{10}O_2$: C, 66.66, H, 7.94;
Found : C, 66.73, H, 8.03%.

5.5.4 General Procedure for Isomerization

The conjugated enelactone (0.05 mmol) and DBU (0.05 mmol) were taken together in $CHCl_3$ [or $CDCl_3$ (0.04 ml) if the reaction were to be monitored by ^1H NMR] and stirred magnetically with monitoring the progress by TLC. The workup involved dilution with $CHCl_3$ (10 ml), washing with cold aq 2% HCl (1 x 4 ml) following H_2O (1 x 4 ml) and brine (1 x 5 ml), in that order. Drying, solvent removal and chromatography over silica gel or chromatogran gave the corresponding isomerized product.

5.5.5 4,5-Dehydro-7-methyl-2-oxepanone 18

Deconjugative isomerization of **17** gave deconjugated enelactone **18** (quantitative) in 5h.

^1H NMR (80 MHz) : ppm 6.0-5.3 (m, 2H, $\underline{H}C = C\underline{H}$), 5.2-4.7 (m, 1H, $-OC\underline{H}CH_3$), 4.0-3.5 (dd, 1H, J = 16 and 3 Hz, $-\underline{H}CC(O)-$), 3.5-2.8 (dd, 1H, J = 16 and 6 Hz, $-C\underline{H}C(O)-$), 2.7-2.1 (bm, 2H, $-C\underline{H}_2CH=CH-$), 1.4 (d, 3H, J = 6 Hz).

IR (neat), ν_{max} : 1725 (C = 0), 1650, 1270, 1050, 780 cm^{-1}.

Mass (m/z) : 126 (M^+).

Analysis calcd.for $C_7H_{10}O_2$: C, 66.66, H, 7.94;
Found : C, 66.55, H, 7.89%.

5.5.6 3-Methyl-6-(2-phenylethyl)tetrahydropyran-2-one 26

A two necked round-bottomed flask (25 ml), flamed and

cooled under N_2, was charged with dry THF (4 ml) and diisopropylamine (0.263 g, 364 μl, 2.6 mmol) and cooled to -80 °C. To it was added n-butyllithium (1.66 ml of 1.3 M solution in hexanes, 2.16 mmol) dropwise (10 min). After 15 min, a solution of lactone **25** (0.34 g, 1.66 mmol; obtained from expt. 3.3.3) in THF (4 ml) was injected dropwise over a period of 10 min. After about 30 min the yellow colored enolate solution was quenched by the addition of methyl iodide (0.30 g, 134 μl, 2.165 mmol) solution in THF (2 ml) and hexamethylphophorous triamide (HMPT; 0.35 g, 393 μl, 2.165 mmol). The resultant was stirred at -80 °C for another 10 min and allowed to come to rt (3h) when it was poured into cold 5% aq HCl solution (7 ml) covered with ether (20 ml). The layers were separated and aq phase extracted with ether (2 x 10 ml). The combined organic extracts were washed with brine (1 x 10 ml), dried and freed of the volatiles to give a residue which upon chromatography furnished the desired product **26** (0.244 g, 67%).

^{1}H NMR (60 MHz) : ppm 7.0 (s, 5H, Ar$\underline{H}$), 4.3-3.8 (m, 1H, -OC$\underline{H}$-), 2.9-2.5 (m, 2H, PhC$\underline{H}_2$-), 2.1-1.35 (m, 7H, 3xC$\underline{H}_2$, >C$\underline{H}$-), 1.3-1.0 [1.2 (d, J = 6 Hz) and 1.1 (d, J = 5 Hz), 3H, -C$\underline{H}_3$ (equatorial and axial)].

IR (KBr), ν_{max} : 1720 (C = 0), 1690, 1440, 1370, 1230, 1205, 1190, 1085, 740 cm^{-1}.

Analysis calcd.for $C_{14}H_{18}O_2$: C, 77.06, H, 8.25;
Found : C, 77.00, H, 8.17%.

5.5.7 3-Benzeneselenenyl-3-methyl-6-(2-phenylethyl)tetrahydropyran--2-one 27

Selenenation of **26** (0.23 g, 1.05 mmol) afforded **27** (0.308 g, 78%).

^{1}H NMR (60 MHz) : ppm 7.8-6.8 (m, 10H, ArH), 4.5-3.7 (m, 1H, -OCH-), 3.0-2.5 (m, 2H, PhCH$_2$-), 2.3-1.2 (m, 6H, 3xCH$_2$), 1.55 (s, 3H, -CH$_3$).

IR (neat), ν_{max} : 1710 (C = 0), 1690, 1235, 1105 and 740 cm^{-1}.

Mass (m/z) : 374 (M^++1), 373 (M^+).

5.5.8 3,4-Dehydro-3-methyl-6-(2-phenylethyl)tetrahydropran-2-one 23a and 3-methylidene-6-(2-phenylethyl)tetrahydropyran-2-one 23b

Dehydroselenenation of **27** (0.221 g, 0.592 mmol) produced **23** (0.128 g, 100%) as 6:4 mix of *endo* and *exo* enelactones (**23a** and **23b**).

Endo enelactone **23a** from a mix of **23a** and **23b** (cf expt. 5.5.9).

^{1}H NMR (80 MHz) : ppm 7.35 (m, 5H, ArH), 6.6 (m, 1H, -HC=C<), 4.6-4.1 (m, 1H, -OCH-), 3.0-2.6 (m, 2H, PhCH$_2$-), 2.5 - 1.7 (m, 7H, -CH$_3$, 2xCH$_2$).

IR (neat), ν_{max} : 1705 cm^{-1} (C=0).

Exo enelactone **23b** from a mix of **23a** and **23b**.

^{1}H NMR (80 MHz) : ppm 7.35 (m, 5H, ArH), 6.5 (q, 1H, J = 2 Hz, -HC=C<), 5.6 (q, 1H, J = 2 Hz, -HC = C<), 4.6 - 4.1 (m, 1H, -OCH-), 3.0-2.6 (m, 4H, PhCH$_2$-, -H$_2$C-CH=C<), 2.1-1.7 (m, 4H, 2xCH$_2$).

IR (neat), ν_{max} : 1715 cm^{-1} (C=0).

Mass (m/z) of mix 23(a,b) : 216 (M^+).

5.5.9 3,4-Dehydro-3-methyl-6-(2-phenylethyl)tetrahydropyran-2-one 23a

Isomerization of mix of **23(a,b)** afforded **23a** (quantitative) after 10h.

^{1}H NMR, IR and mass spectra are identical to that shown in expt. 5.5.8.

Analysis calcd.for $C_{14}H_{16}O_2$: C, 77.77, H, 7.41;
Found : C, 77.68, H, 7.50%.

5.5.10 2-Benzyl-2-carbomethoxycyclohexanone 28

DBU (1.55 g, 1.52 ml, 10.2 mmol) was added dropwise (15 min) to a solution of 2-carbomethoxycyclohexanone (1.56 g, 10 mmol) in dry DMF (7 ml) at 0 ^{o}C under N_2. After 10 min, a solution of benzyl bromide (1.744 g, 10.2 mmol) in DMF (2 ml) was added dropwise (10 min), and the resultant allowed to come to rt. followed by heating to 70 ^{o}C for 6h. The reaction mix was brought to rt, poured into an ice cold H_2O (30 ml) and extracted with ether (3 x 40 ml). The combined ether extracts was washed successively with cold 2% aq HCl (1 x 20 ml), water (1 x 25 ml) and brine (1x25 ml). Drying, evaporation of solvent and chromatography of the residue furnished **28** (2.04 g, 83%).

^{1}H NMR (60 MHz) : ppm 7.0 (s, 5H, Ar$\underline{H}$), 3.45 (s, 3H, -$CO_2C\underline{H}_3$), 3.4-2.5 [3.15 (d, J = 14 Hz), 2.7 (d, J = 14 Hz), 2H, Ph$C\underline{H}_2$-], 2.5-2.0 (m, 2H, -$C\underline{H}_2$C(O)-), 2.0-1.0 (m, 4H, 2x$C\underline{H}_2$).

IR (neat), ν_{max} : 1720 (ester C=0), 1700 (ring C=0), 1600, 1490 and 1090 cm^{-1}.

Analysis calcd.for $C_{15}H_{18}O_3$: C, 73.17, H, 7.32;
Found : C, 73.28, H, 7.40%.

5.5.11 2-Benzylcyclohexanone 29

Dealkyldecarboxylation of **28** (2.46 g, 10.0 mmol) following the procedure as described for expt. 3.3.2 in Chapter 3 afforded **29** (1.54 g, 82%).

^{1}H NMR (60 MHz) : ppm 7.0 (s, 5H, Ar$\underline{H}$), 3.5-2.7 (m, 1H, >C$\underline{H}$-), 2.6-1.0 (m, 10H, 5 x $C\underline{H}_2$).

IR (neat), ν_{max} : 1700 (C=0), 1590, 1440, 1120 and 780 cm^{-1}.

Analysis calcd.for $C_{13}H_{16}O$: C, 82.98, H, 8.51;
Found : C, 83.09, H, 8.39%.

5.5.12 7-Benzyl-2-oxepanone 30

Baeyer-Villiger oxidation of **29** (0.376 g, 2.0 mmol) afforded **30** (0.408 g, 100%).

^{1}H NMR (60 MHz) : ppm 7.15 (s, 5H, Ar$\underline{H}$), 4.6-3.9 (m, 1H, -OC$\underline{H}$<), 3.0-2.3 (m, 4H, PhC$\underline{H}_2$-), -$\underline{H}_2$CC(O)-), 2.0-1.1 (m, 6H, 3xC$\underline{H}_2$).

IR (neat), ν_{max} : 1720 (C=0), 1600, 1490, 1450, 1340, 1320, 1275, 1250, 1170, 1010 and 750 cm^{-1}.

Mass (m/z) : 204 (M^+).

Analysis calcd.for $C_{13}H_{16}O_2$: C, 76.47, H, 7.84;
Found : C, 76.58, H, 7.71%.

5.5.13 3-Benzeneselenenyl-7-benzyl-2-oxepanone 31

Selenenation of **30** (0.408 g, 2.0 mmol) produced **31** (0.517 g, 72%), as 1:1 mix of *cis* and *trans* isomers **31a** and **31b**,

respectively, which were separated by chromatography over silica gel.

Cis selenolactone **31a**

^{1}H NMR (400 MHz) : ppm 7.56 (dd, 2H, J = 7 and 3 Hz, *meta* H ArSe-), 7.46-7.19 (m, 8H, ArH), 4.50 (m, 1H, -OCH<), 4.20 (dd, 1H, J = 12 and 2 Hz, -SeCH<), 3.1 (dd, 1H, J = 12 and 6 Hz, PhCH<), 2.82 (dd, 1H, J = 12 and 6 Hz, PhCH<), 2.12 (bd, 1H, J = 13 Hz, C_6-H), 2.0 - 1.81 (m, 3H, C_6-H, CH_2), 1.58-1.49 (m, 1H, methylene-H), 1.48-1.34 (m, 1H, methylene-H).

IR (neat), ν_{max} : 1710 (C=0), 1600, 1575, 1435, 1310, 1250, 1190 and 1020 cm^{-1}.

Mass (m/z) : 359 (M^+).

Trans selenolactone **31b**

^{1}H NMR (400 MHz) : ppm 7.50 (d, 2H, J = 7 Hz, *meta*,HArSe-), 7.39 - 7.20 (m, 8H, ArH), 5.23 (m, 1H, -OCH<), 4.22 (t, 1H, J = 4 Hz, -SeCH<), 3.10 (dd, 1H, J = 12 and 6 Hz, PhCH-), 2.86 (dd, 1H, J = 12 and 6 Hz, PhCH-), 2.12 (m, 2H, CH_2), 2.0 (td, 1H, J = 12 and 3 Hz, methylene-H), 1.9 - 1.75 (m, 2H, $>CH_2$), 1.65 - 1.55 (m, 1H, methylene H).

IR (neat),ν_{max} : 1710 (C=0), 1600, 1570, 1445, 1280, 1245, 1180, 1020, 790 cm^{-1}.

Mass (m/z) : 359 (M^+).

5.5.14 7-Benzyl-3,4-dehydro-2-oxepanone 32

Dehydroselenenation of **31(a,b;** 0.36 g, 1.0 mmol) gave **32** (0.14 g, 70%).

^{1}H NMR (80 MHz) : ppm 7.3 (s, 5H, ArH), 6.6-6.3 (td, 1H, J = 12 and 4 Hz, -HC=CHC(O)-), 6.1-5.9 (td, 1H, J = 12 and 1.2 Hz, -HC=CHC(O)-), 4.4-3.6 (m, 1H, -OCH<), 3.18 (dd, 1H, J = 13 and 5.5 Hz, PhCH-), 2.88 (dd, 1H, J = 13 and 5.5 Hz, PhCH-), 2.6-2.2 (m, 2H, -H_2C.CH=), 2.16- 2.0 (m, 2H, CH_2).

IR (neat), ν_{max} : 1700 (C=0), 1600, 1490, 1390, 1285, 1190, 1040 and 780 cm^{-1}.

Mass (m/z) : 202 (M^+).

Analysis calcd. for $C_{13}H_{14}O_2$: C, 77.23, H, 6.93;
Found : C, 77.33, H, 7.05%.

5.5.15 7-Benzyl-4,5-dehydro-2-oxepanone 33

Deconjugative isomerization of **32** (0.12 g, 0.594 mmol) gave, after 3h **33** (0.103 g, 86%) and rest of starting material intact. The product material **33** was purified by radial chromatography.

^{1}H NMR (80 MHz) : ppm 7.3 (s, 5H, ArH), 5.9-5.3 (m, 2H, -HC=CH-), 5.10-4.7 (m, 1H, -OCH<), 3.9- 3.5 (m, 1H, -(O)CCH-CH=CH-), 3.6-2.6 (m, 3H, -(O)CCHCH=CH-, PhCH_2-), 2.5-2.2 (m, 2H, CH_2).

IR (neat), ν_{max} : 1720 (C=0), 1650, 1600, 1490, 1445, 1390, 1215, 1210, 1140, 1030 and 700 cm^{-1}.

Mass (m/z) : 202 (M^+).

5.5.16 7-Benzyl-4,5-epoxy-2-oxepanone 34 (*cis*) and 38 (*trans*)

To a stirred solution of **33** (0.044 g, 0.217 mmol) in $CHCl_3$ (0.4 ml) at 5 ^oC was added perbenzoic acid (0.56 ml of a 0.5 M solution 0.28 mmol) and the resultant mix allowed to come to rt. and stirred for 15h. Saturated aq Na_2SO_3 (3 ml) was added and stirred for 30 min. The reaction mix was partitioned between $CHCl_3$ (15 ml) and water (5 ml). The layers were separated and the aq layer extracted with $CHCl_3$ (2 x 5 ml). The combined organic extracts was washed with 10% aq $NaHCO_3$ (2 x 7ml) and brine (1 x 7 ml). Drying, removal of solvents, and chromatographic purification furnished *cis* isomer **34** (0.028 g, 60%) and *trans* isomer (0.014 g, 30%).

Cis epoxy lactone **34**

m p : 78 - 79 ^oC

^1H NMR (400 MHz) : ppm 7.35-7.15 (m, 5H, ArH), 4.31 ()m, 1H, -OCH<), 3.29 (m, 1H, oxirane-H), 3.20-3.10 (m, 2H, $-H_2CC(O)-$), 3.05 (dd, 1H, J = 12 and 6 Hz, PhCH-), 2.96 (dd, 1H, J = 13 and 4 Hz, oxirane-H), 2.85 (dd, 1H, J = 12 and 6 Hz, PhCH-), 2.45 (d, 1H, J = 13 Hz, ring methylene-H), 2.16 (ddd, 1H, J = 13, 8 and 3 Hz, ring methylene-H).

IR (KBr), ν_{max} : 1720 (C=0), 1590, 1270, 1160, 1140, 1110, 900 and 695 cm^{-1}.

Mass (m/z) : 218 (M^+).

Analysis calcd.for $C_{13}H_{14}O_3$: C, 71.56, H, 6.42;

Found : C, 71.61, H, 6.37%.

Trans epoxylactone **38**

m p : 86 - 87 °C.

^{1}H NMR (400 Mhz) : ppm 7.35-7.2 (m, 5H, ArH), 4.66 (m, 1H, -OCH<), 3.41 (unsymm. d, 1H, J = 15 Hz, >HCC(O)-), 3.30 (dd, 1H, J = 15 and 6 Hz, >HCC(O)-), 3.2 (m, 2H, 2xoxirane-H), 3.05 (dd, 1H, J = 13 and 6 Hz, PhCH-), 2.78 (dd, 1H, J = 13 and 6 Hz, PhCH), 2.37 (dd, 1H, J = 17 and 12 Hz, ring methylene-H), 2.18 (m, 1H, ring methylene-H).

IR (KBr), ν_{max} : 1730 (C=0), 1590, 1360, 1285, 1255, 1180, 1050, 750 and 700 cm^{-1}.

Mass (m/z) : 218 (M^+).

Analysis calcd.for $C_{13}H_{14}O_3$: C, 71.56, H, 6.42;
Found : C, 71.61, H, 6.49%.

5.5.17 7-Benzyl-3,4-dehydro-5-hydroxy-2-oxepanone 35 and 7-benzyl-2,6-dioxa-3-oxobicyclo[3.3.0]octane 39

To a solution of **34** (0.048 g, 0.22 mmol) in DMF (1.0 ml) was added K_2CO_3 (0.09 g, 0.66 mmol). The mix was stirred at rt for 2h and 5 ml water added. The reaction mix was extracted thoroughly with EtOAc (3 x 10 ml). The combined extracts was washed with brine (1 x 5 ml), dried and concentrated. The residue was chromatographed to afford **35** (0.036 g, 75%) and bicyclic species **39** (0.01 g, 20%).

Hydroxy enelactone 35

^{1}H NMR (60 MHz, $CDCl_3$) : ppm 7.15 (s, 5H, ArH), 6.25 (dd, 1H, J = 12 and 3 Hz, -HC=CHC(O)-), 5.7 (dd,

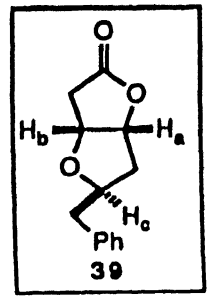
1H, J = 12 and 1 Hz, -CH=CHC(O)-), 4.9 -4.2 (m, 2H, 2 x -OCH<), 3.4 (bs, 1H, -OH), 2.9 (dd, 2H, J = 14 and 6 Hz, $PhCH_2$-), 2.3-1.9 (m, 2H, ring methylene-H).

IR (neat), ν_{max} : 3420 (OH), 1695 (C=0), 1625, 1490, 1450, 1300 and 1050 cm^{-1}.

Mass (m/z) : 218 (M^+).

Analysis calcd.for $C_{13}H_{14}O_3$: C, 71.56, H, 6.42;
Found : C, 71.41, H, 6.29%.

Bicyclic compound 39



39

^1H NMR (400 MHz) : ppm 7.35-7.15 (m, 5H, ArH), 5.10 (t, 1H, J = 4 Hz, H_a), 4.81 (t, 1H, J = 4 Hz, H_b), 4.37 (m, 1H, H_c), 2.95 (dd, 1H, J = 12 and 6 Hz, PhCH-), 2.85 (dd, 1H, J = 12 and 6 Hz, PhCH-), 2.75 (dd, 1H, J = 18 and 6 Hz, -HCC(O)-), 2.65 (dm, 1H, J = 18 Hz, -HCC(O)-), 2.34 (dd, 1H, J = 12 and 4 Hz, ring methylene-H), 1.76 (ddd, 1H, J = 12, 9 and 4 Hz, ring methylene-H).

IR (neat), ν_{max} : 1770 (5-membered ring C=0), 1590, 1445, 1060, 1030 and 750 cm^{-1}.

Mass (m/z) : 218 (M^+).

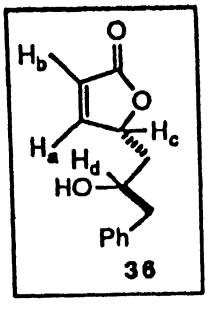
Analysis calcd. for $C_{13}H_{14}O_3$: C, 71.56, H, 6.42;

Found : C, 71.61, H, 6.48%.

5.5.18 3,4-Dehydro-5-(2-hydroxy-3-phenylethyl)-1-oxa-2-oxocyclopentane 36

To a solution of 7-membered hydroxy enelactone **35** (0.032 g, 0.146 mmol) in THF (2 ml) was added, at 5 °C, 1.2 ml of 1% aq NaOH (0.29 mmol). After stirring for 1h the reaction mix was acidified to pH 4 with 2% aq HCl. This was stirred for 30 min when the reaction solution was extracted with EtOAc (3 x 10 ml). The combined organic extracts was washed with brine (1 x 10 ml), dried and concentrated to furnish a residue which was chromatographed to give **36** (0.018 g, 56%) and the bicyclic species **39** (0.009 g, 28%).

5-membered enelactone **36**



36

^{1}H NMR (80 MHz) : ppm 7.6 (dd, 1H, J = 5 and 1.5 Hz, $\underline{H}_a$), 7.25 (m, 5H, Ar$\underline{H}$), 6.1 (dd, 1H, J = 5 and 2.0 Hz, $\underline{H}_b$), 5.3 (tt, 1H, J = 6.5 and 1.5 Hz, $\underline{H}_c$) 4.0 (m, 1H, $\underline{H}_d$), 2.85 (m, 3H, O$\underline{H}$, PhC$\underline{H}_2$-), 2.0 (t, 2H, J = 5 Hz, -C$\underline{H}_2$).

IR (neat), ν_{max} : 3340 (OH), 1740 (unsaturated C=O in γ-lactone), 1590, 1445, 1160 and 810 cm^{-1}.

Mass (m/z) : 218 (M^+).

Analysis calcd. for $C_{13}H_{14}O_3$: C, 71.56, H, 6.42;

Found : C, 71.61, H, 6.36%.

5.5.20 Treatment of 36 with t-BuOOH and DBU

To a solution of DBU in dichloroethane (200 μl) was added t-BuOOH (34 μl of 2.35 M solution in dichloroethane, 0.082 mmol) followed by, after 5 min, a solutionof **36** (0.009 g, 0.041 mmol) in dichlroethane (500 μl) and the resultant stirred for 20 min. Solvent was removed and the residue passed through a short silica gel column to furnish only the bicyclic material **39** (0.009 g, 100%).

5.5.21 Reaction of 36 with phenoxythiocarbonyl chloride (PTC-Cl)

To a solution of **36** (0.015 g, 0.068 mmol) in dry dichloromethane (500 μl) were added, at 5 ^oC and under N_2, dry pyridine (0.02 g, 0.251 mmol), DMAP (one small crystal) and PTC-Cl (0.013 g, 0.075 mmol) and the resultant mix stirred for 8h. The reaction mix was diluted with EtOAc (10 ml) and washed with cold 1% aq HCl (1 x 2 ml) and brine (1 x 3 ml). Drying, evaporation of volatiles and chromatography of the residue gave bicyclic species **39** (0.007 g, 46%) and the remaining starting material **36** intact.

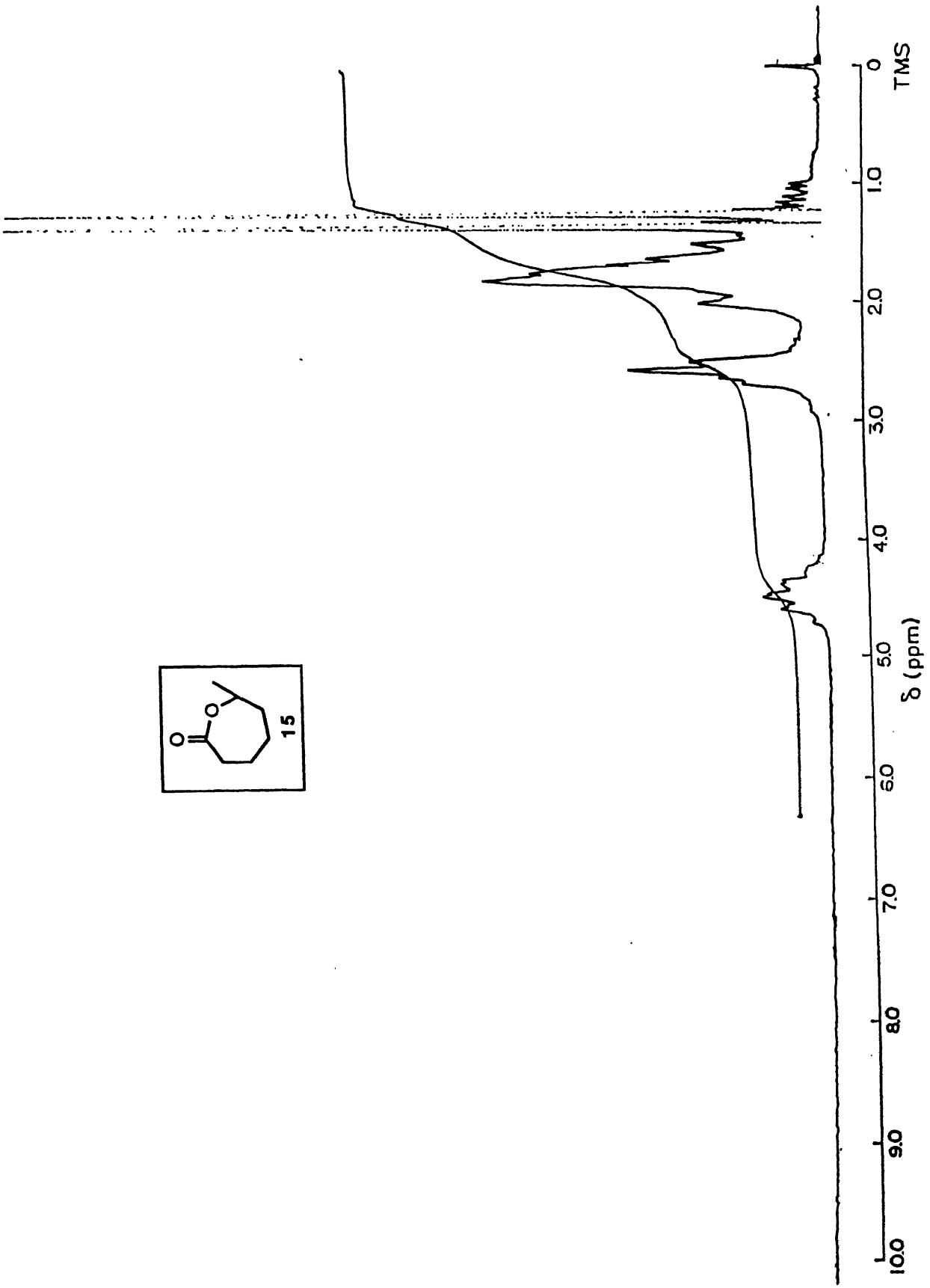


Fig. 5.1 ^{1}H NMR spectrum (60 MHz) of **15**

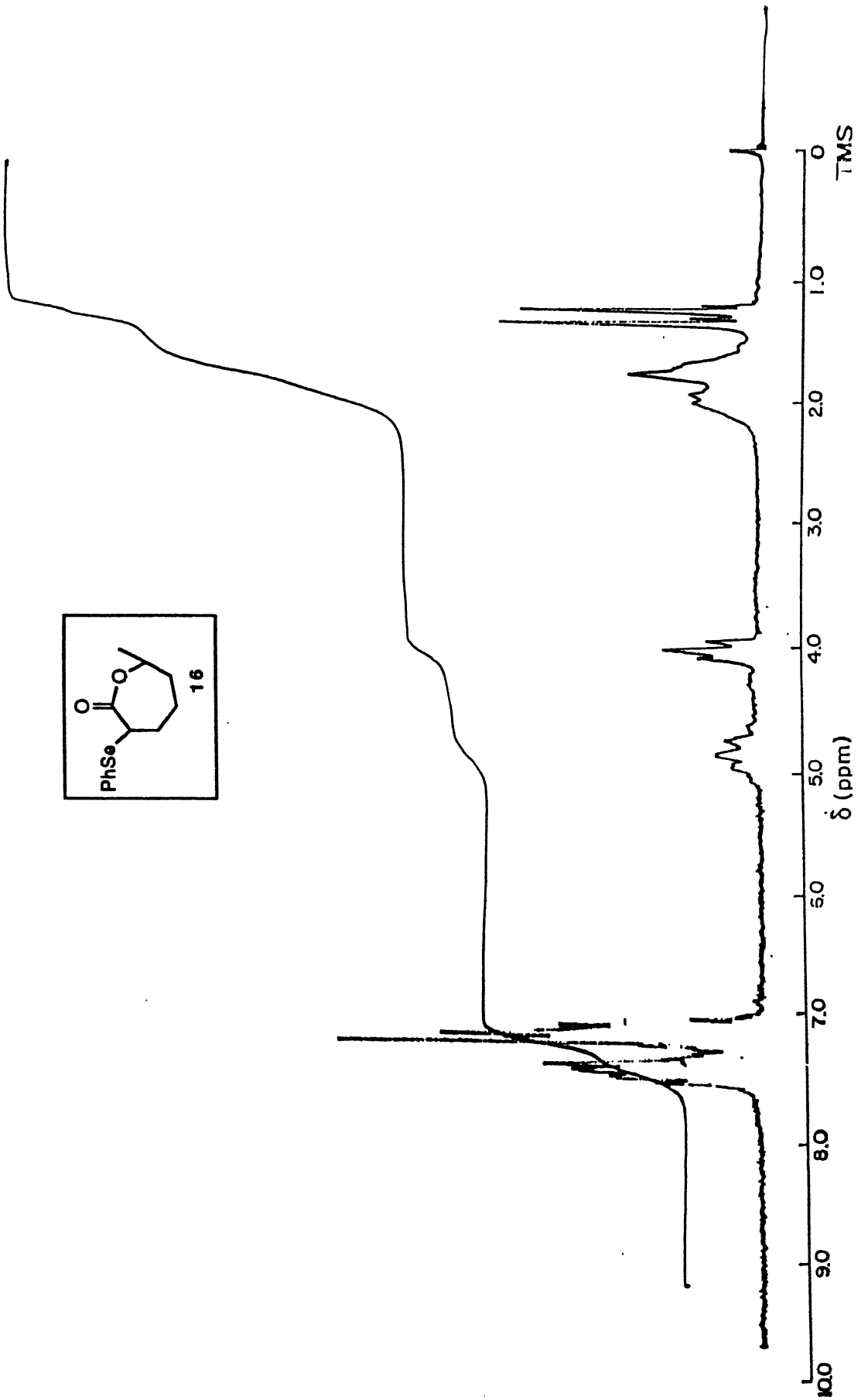


Fig. 5.2 ^{1}H NMR spectrum (60 MHz) of 16

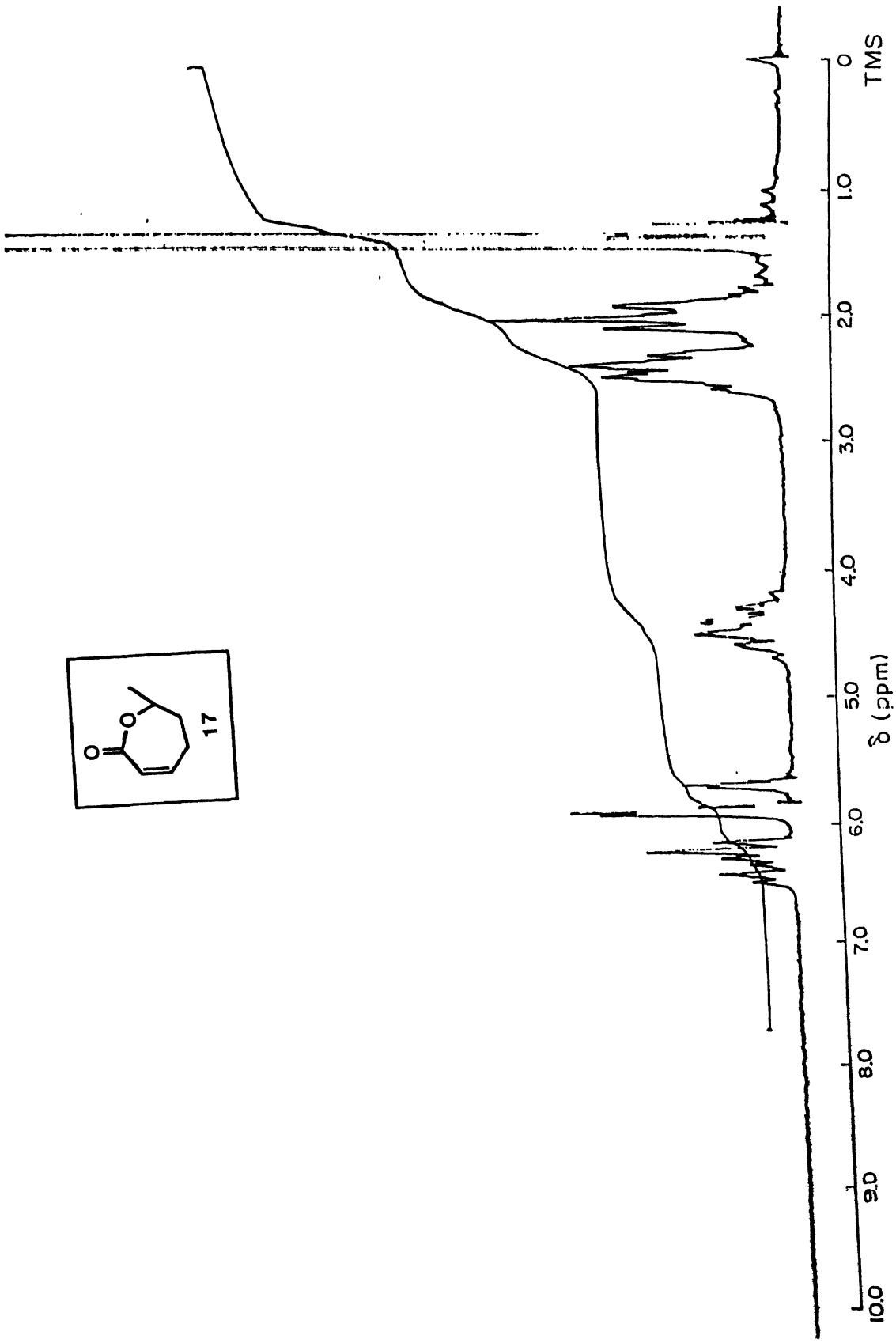


Fig. 5.3 ^{1}H NMR spectrum (60 MHz) of 17

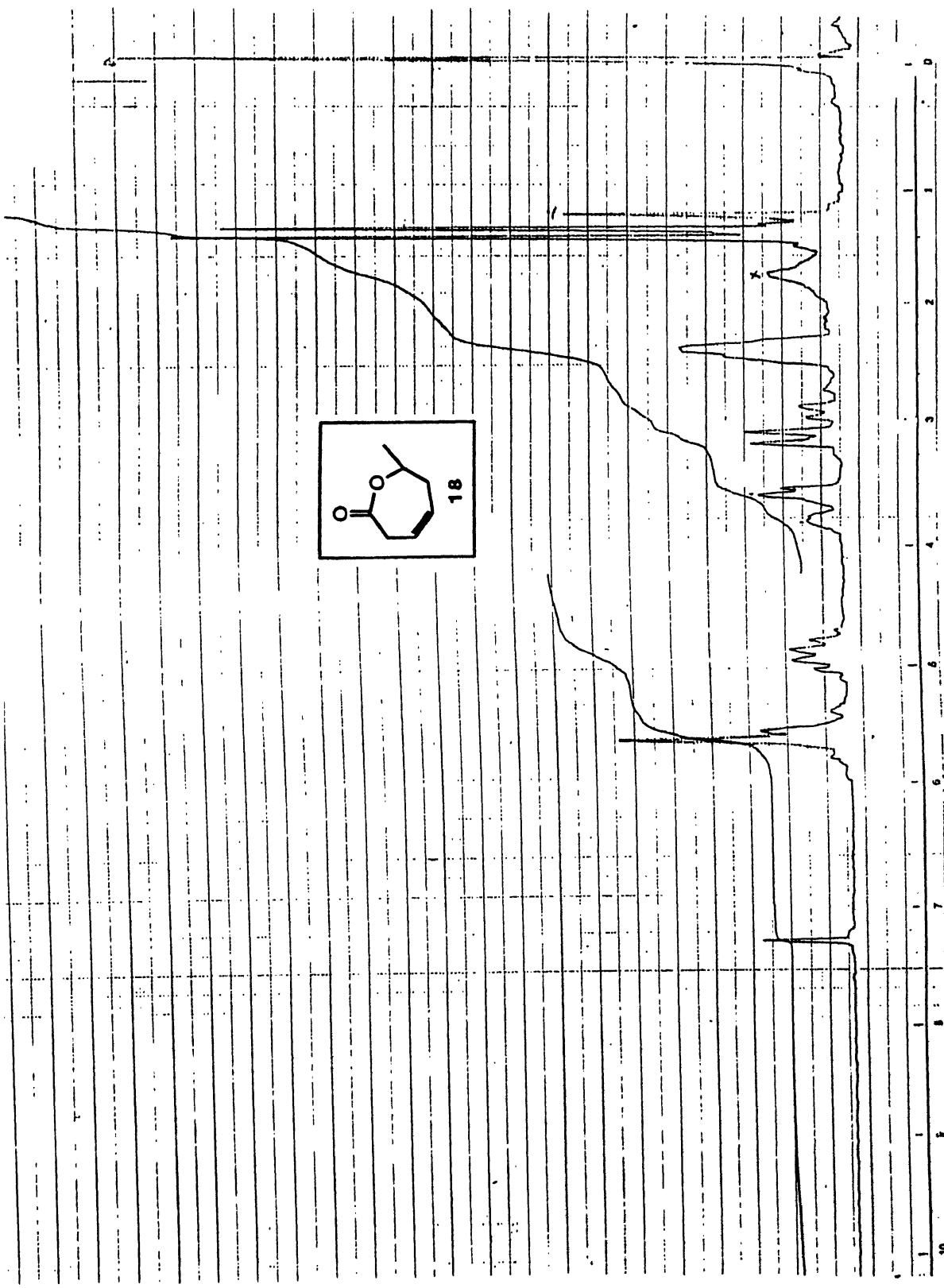


Fig. 5.4 ^{1}H NMR spectrum (80 MHz) of 18

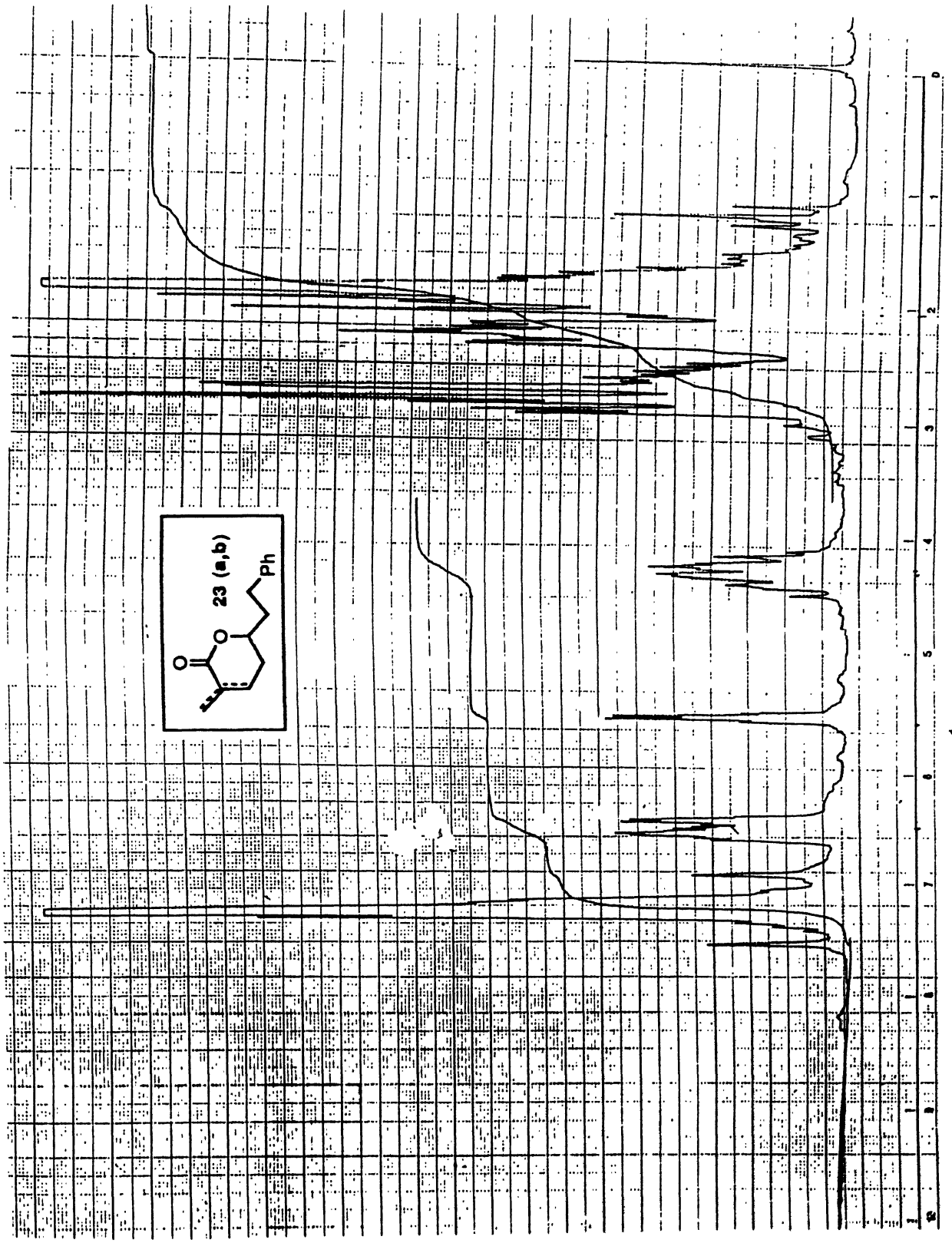


Fig. 5.5 ^{1}H NMR spectrum (80 MHz) of 23(a,b)

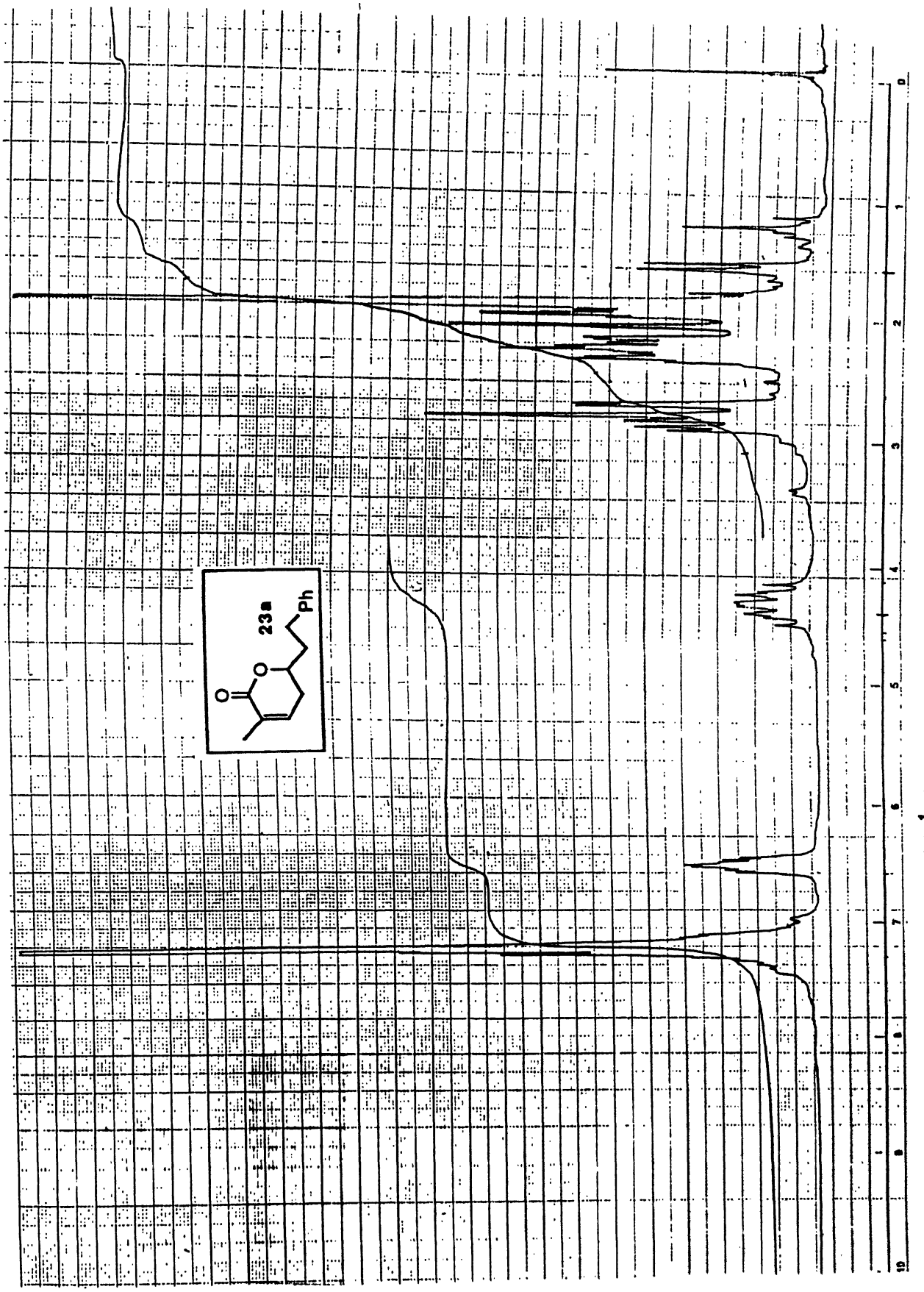


Fig. 5.6 ^{1}H NMR spectrum (80 MHz) of 23a

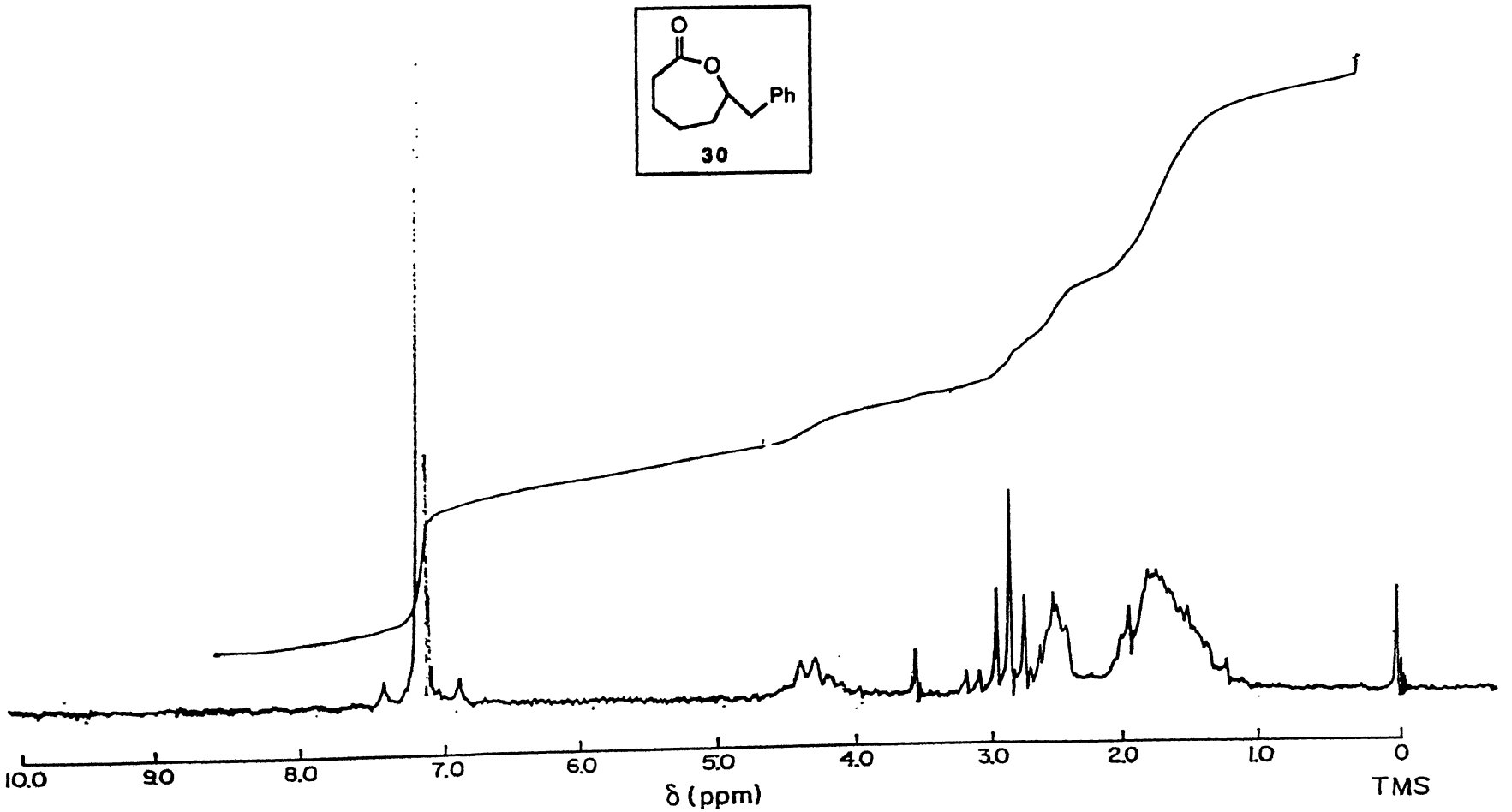


Fig. 5.7 ^{1}H NMR spectrum (60 MHz) of **30**

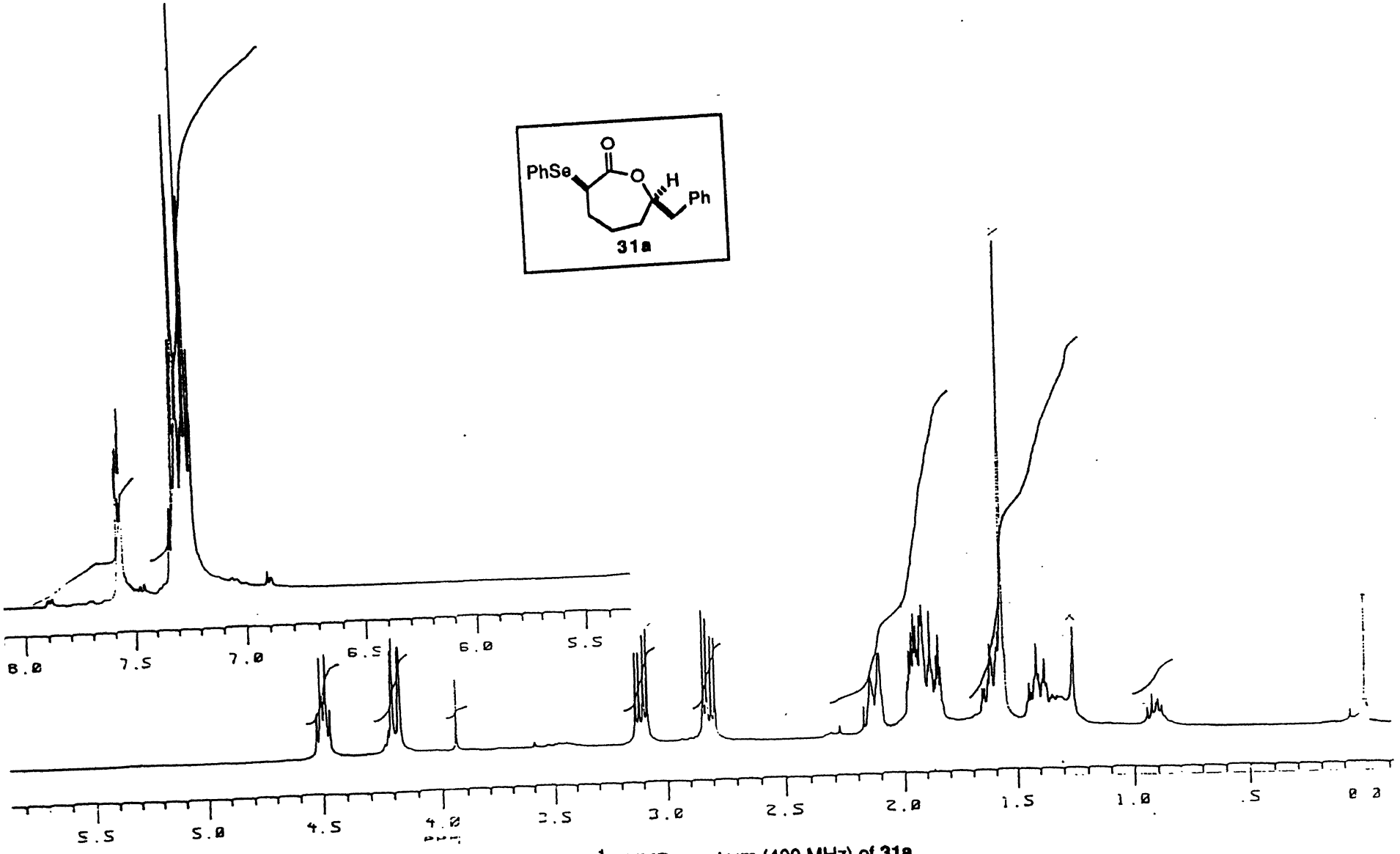


Fig. 5.8 ^{1}H NMR spectrum (400 MHz) of **31a**

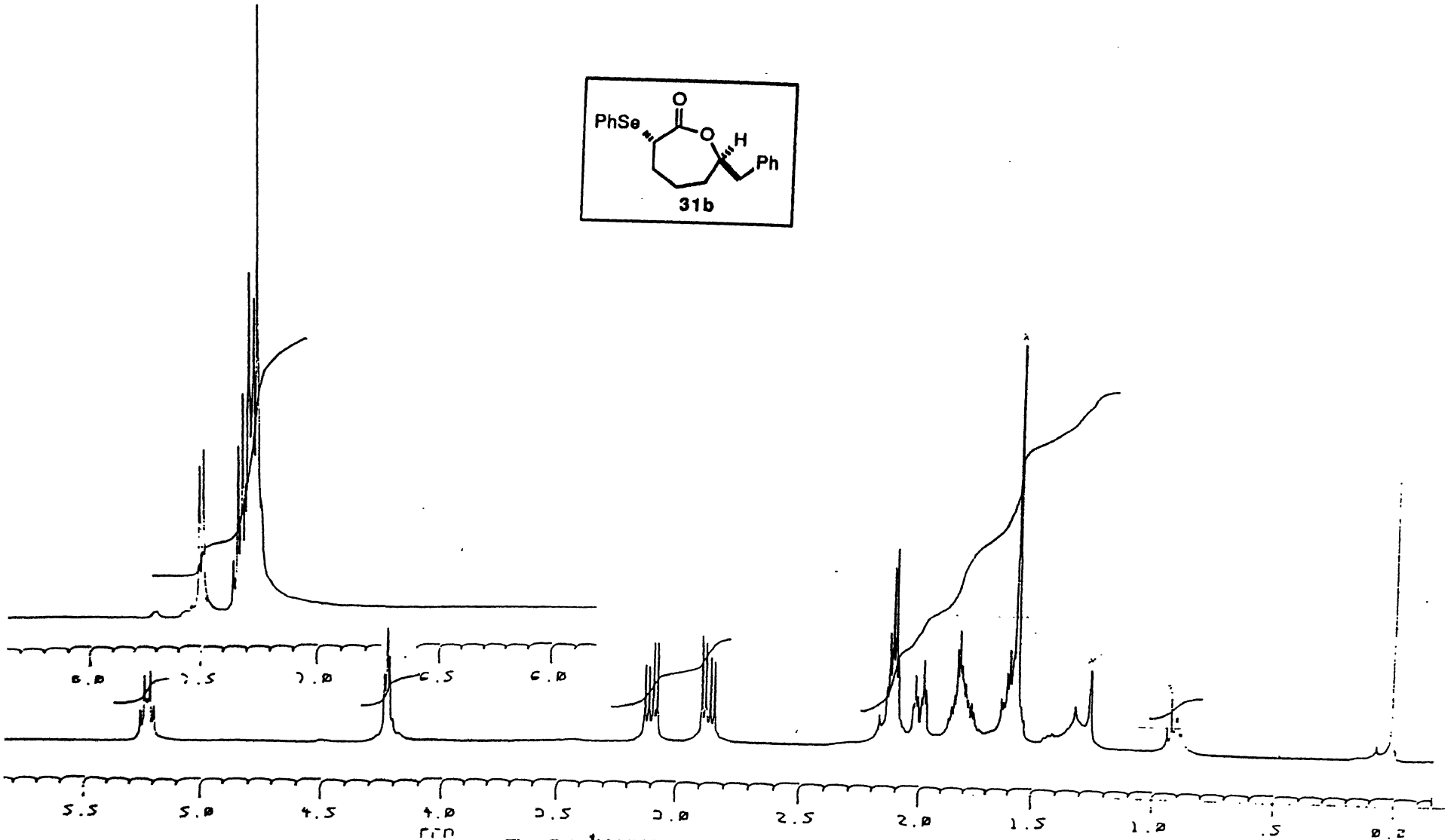


Fig. 5.9 ^{1}H NMR spectrum (400 MHz) of **31b**

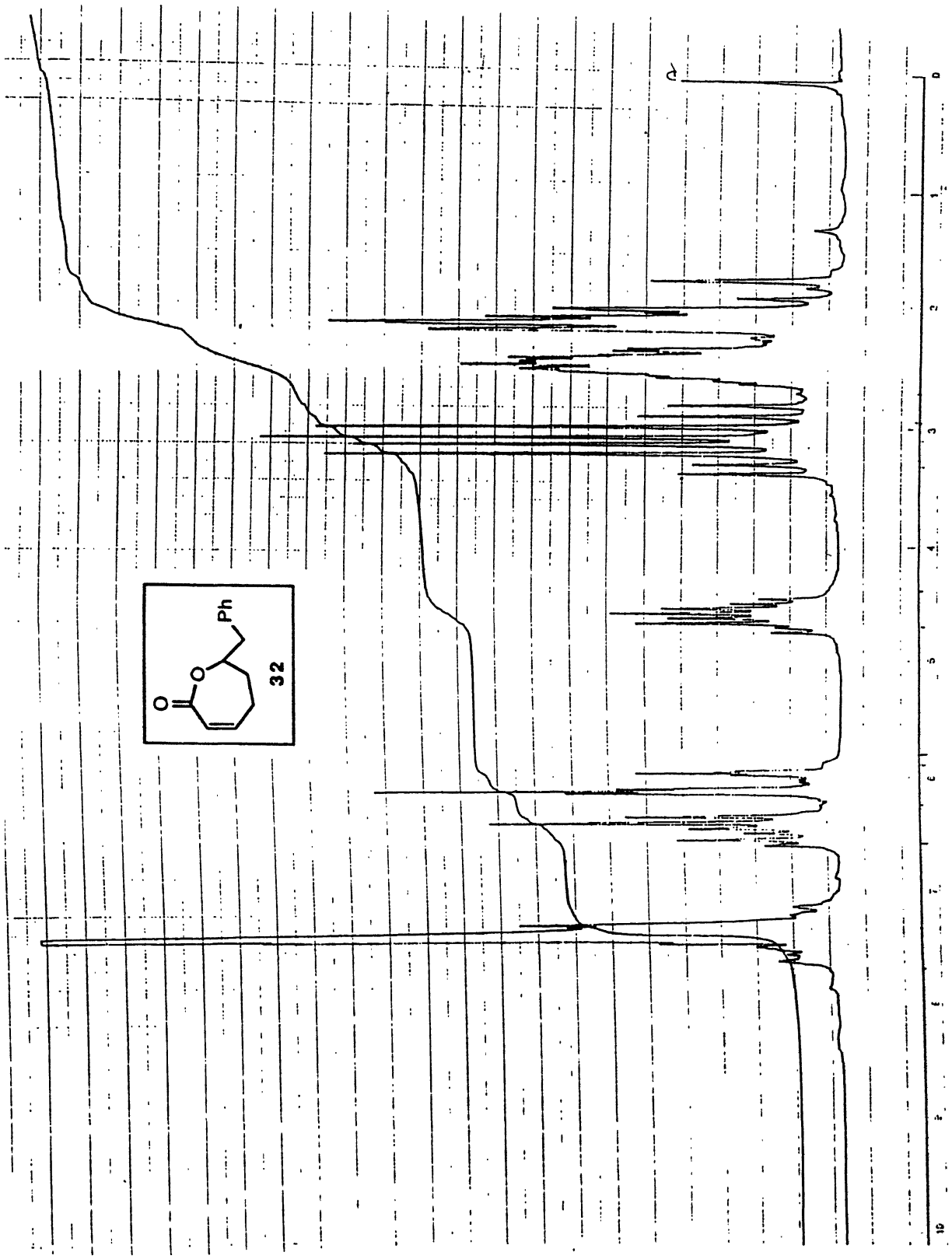


Fig. 5.10 ^{1}H NMR spectrum (80 MHz) of **32**

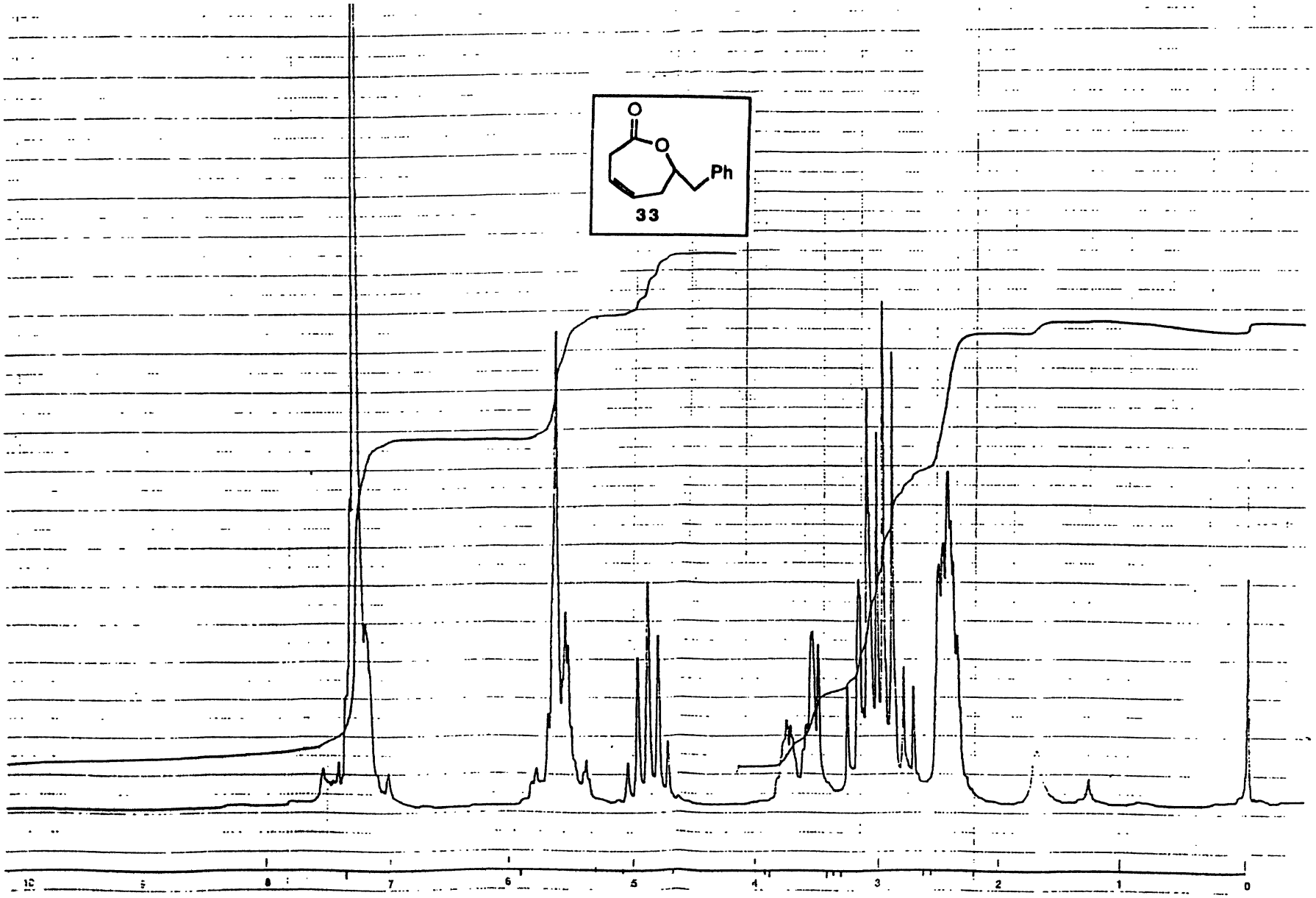


Fig. 5.11 ^{1}H NMR spectrum (80 MHz) of 33

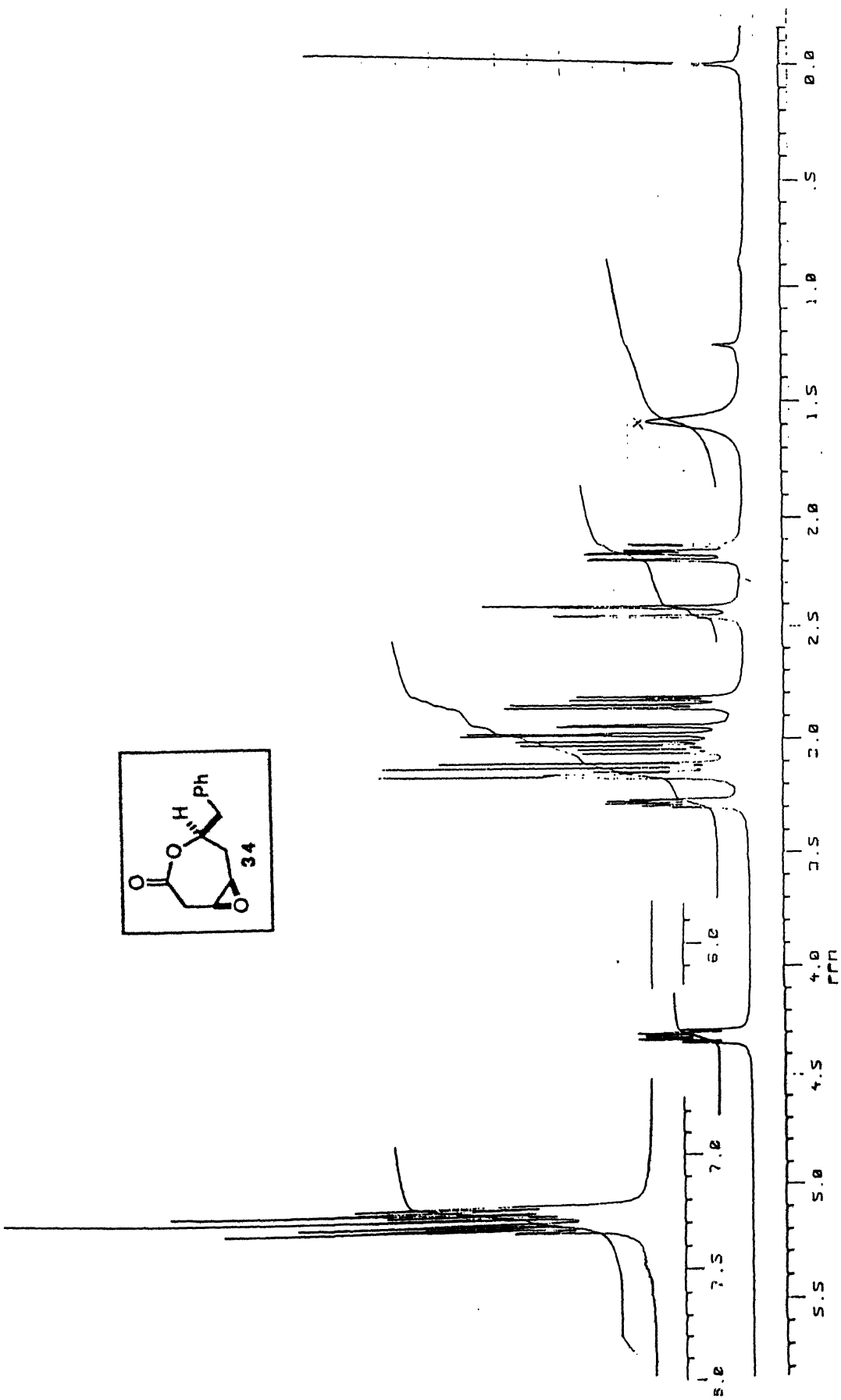


Fig. 5.12 ^{1}H NMR spectrum (400 MHz) of **34**

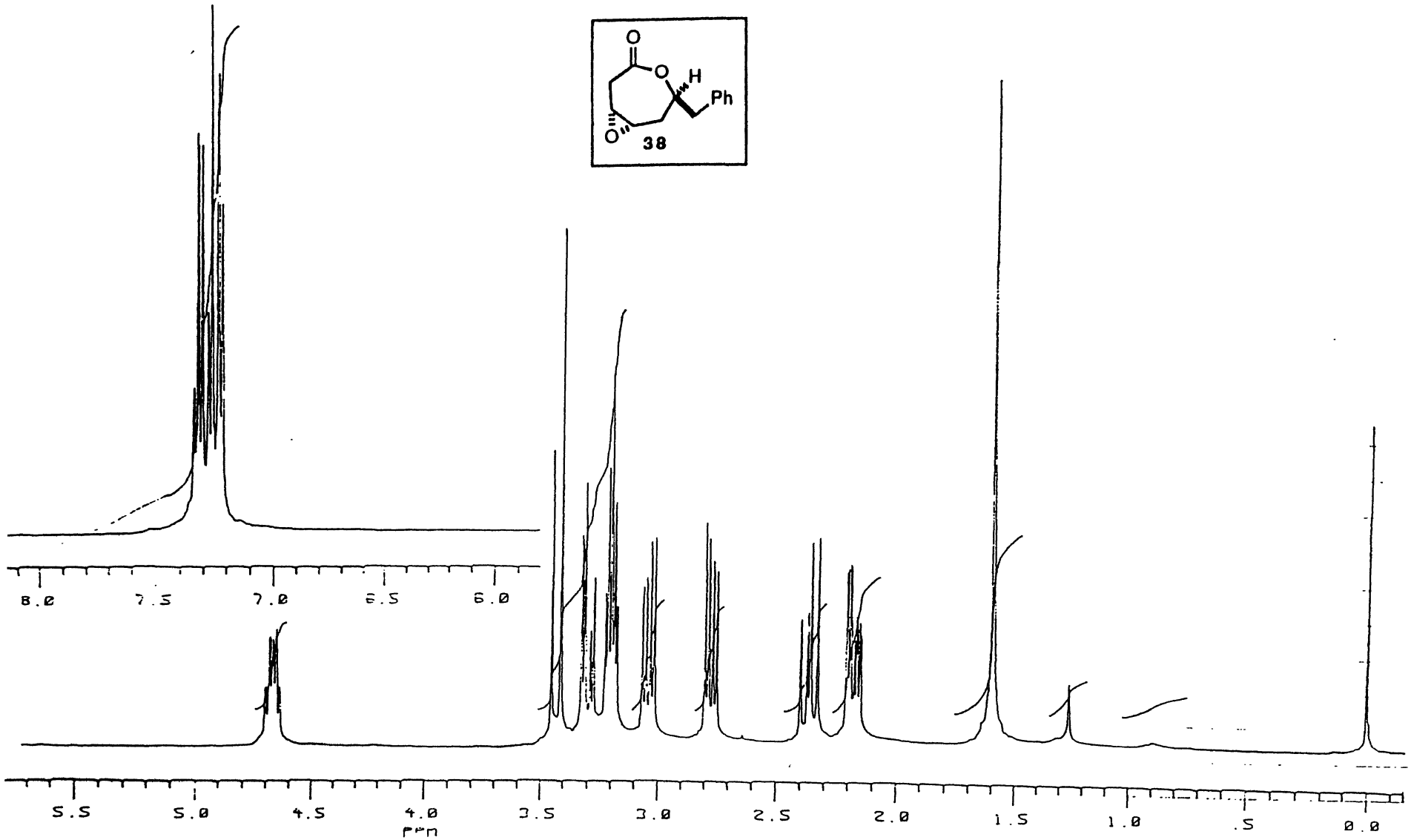


Fig. 5.13 ^{1}H NMR spectrum (400 MHz) of **38**

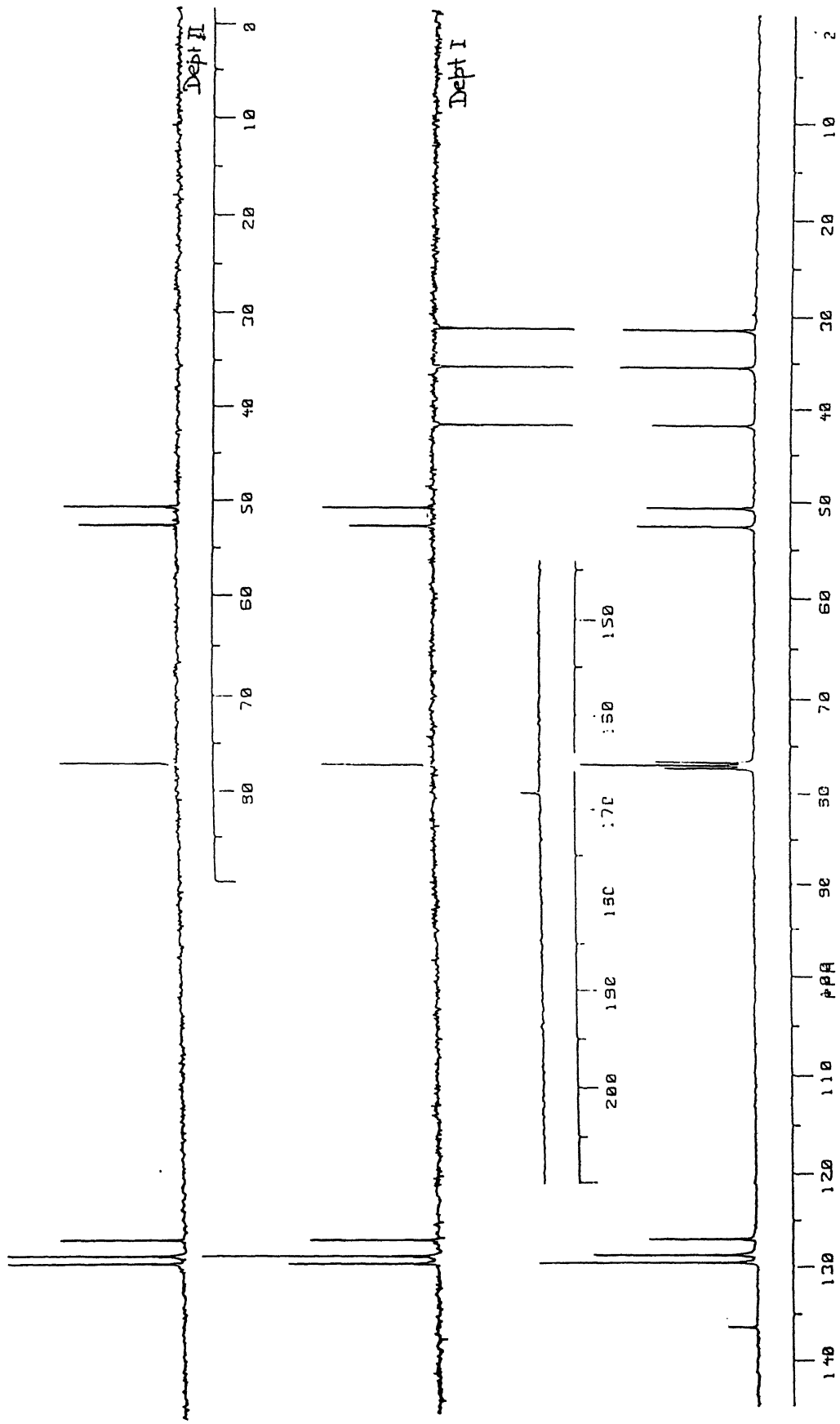


Fig. 5.14 ^{13}C NMR spectrum (400 MHz) of **38**

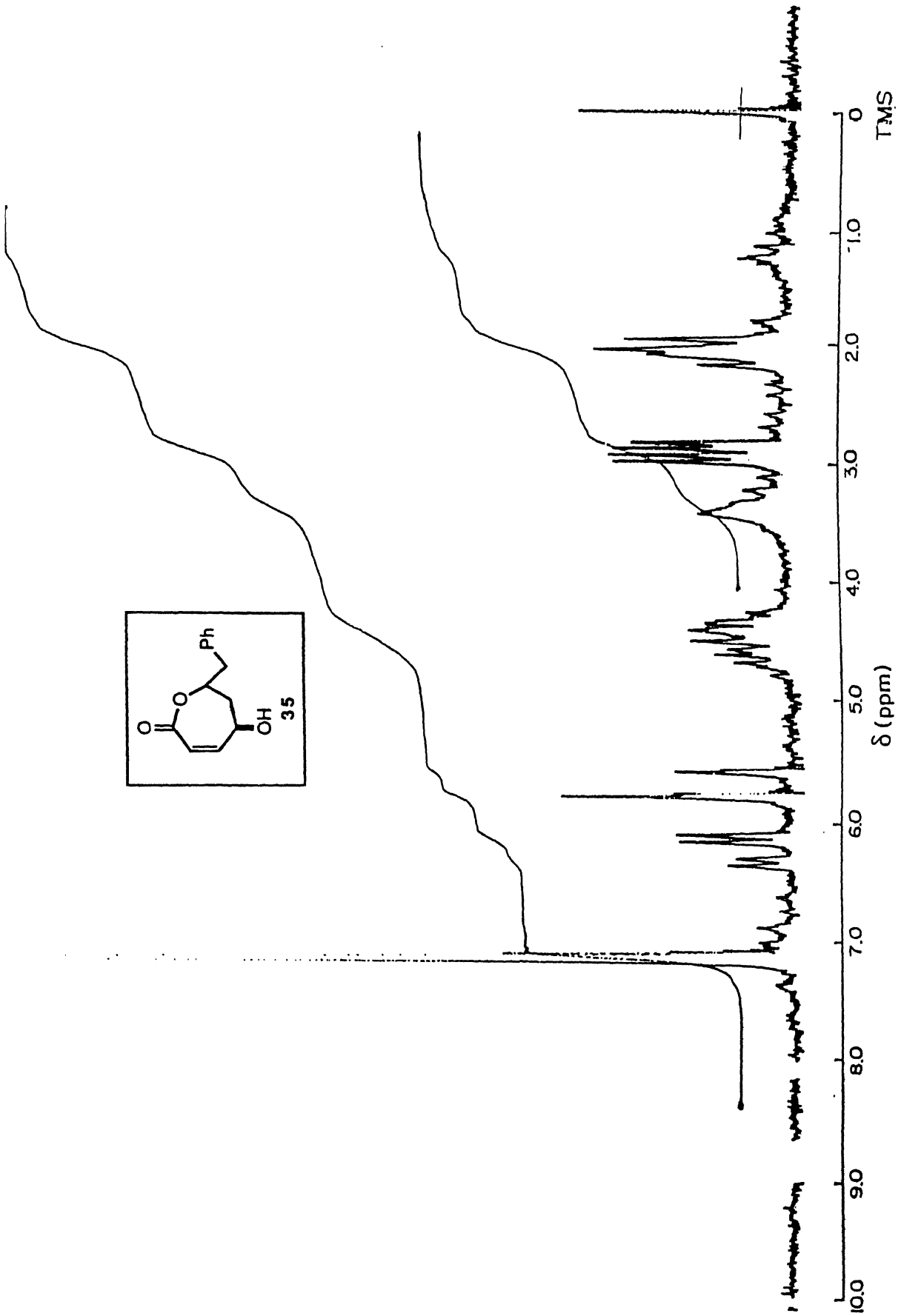


Fig. 5.15 ^{1}H NMR spectrum (60 MHz) of **35**

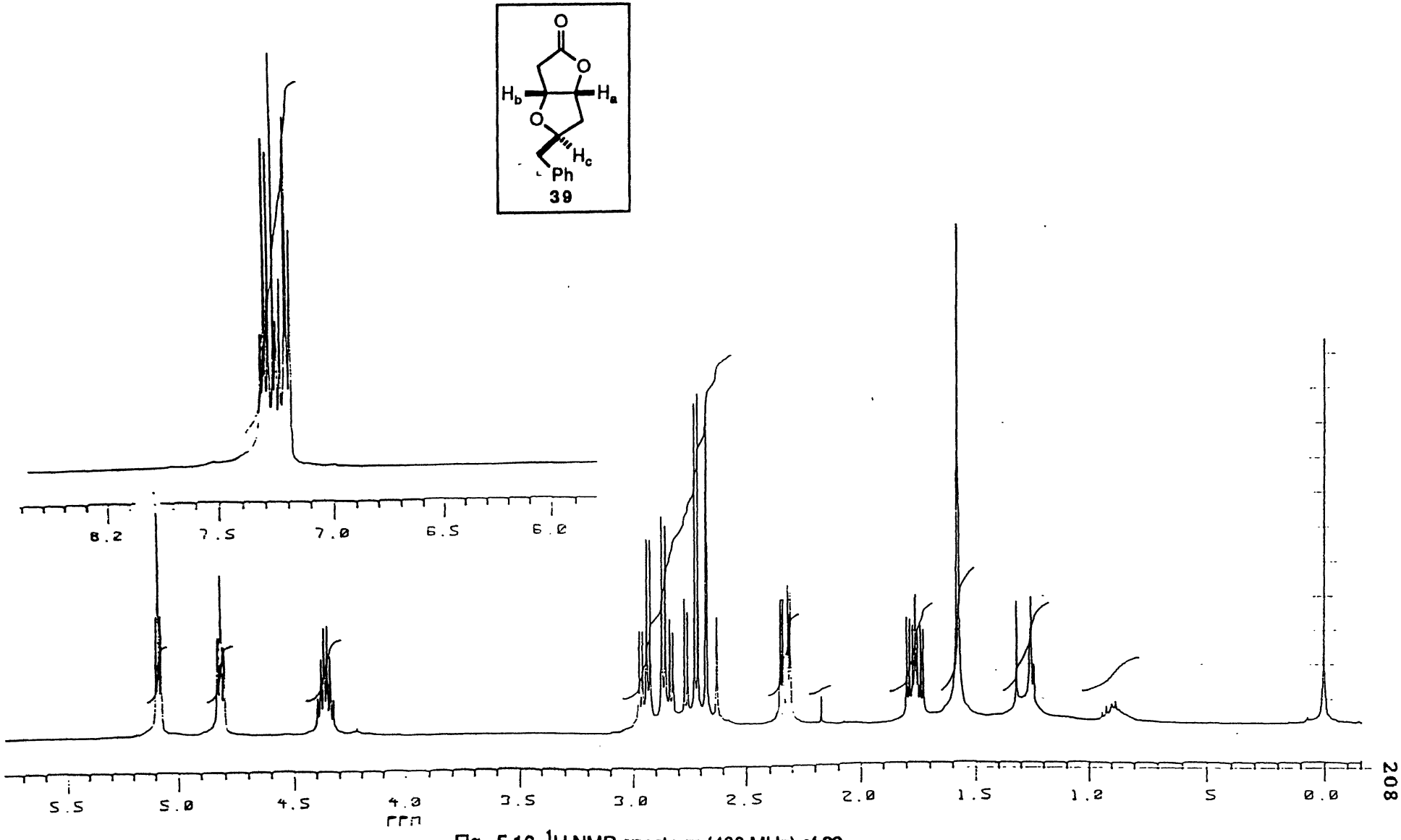


Fig. 5.16 ^{1}H NMR spectrum (400 MHz) of **39**

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